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This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (280 characters max)

METHOD TO TREAT FUNCTIONAL SOMATIC SYNDROMES AND FOR DIAGNOSING A PATIENT BASED ON A FUNCTIONAL SOMATIC SYNDROME SYMPTOM

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ENCLOSED APPLICATION PARTS *(check all that apply)*

20 Number of Pages in Specification — Other (specify) Appendix A (9 pp.) and Appendix B (5 dsp.)

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METHOD OF PAYMENT *(check all that apply)*

X A check or money order is enclosed to cover the Provisional filing fees ($150.00 Large Entity; $75.00 Small Entity).
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
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Respectfully submitted,

SIGNATURE _____ Date January 9, 2003

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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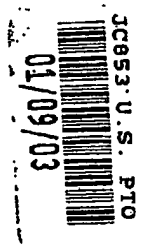

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	ATTORNEY'S DOCKET NUMBER
AVRAM R. GOLD	**2111/030019**

ENTITLED

"METHOD TO TREAT FUNCTIONAL SOMATIC SYNDROMES AND FOR DIAGNOSING A PATIENT BASED ON A FUNCTIONAL SOMATIC SYNDROME SYMPTOM"

BOX PROVISIONAL PATENT APPLICATION
COMMISSIONER FOR PATENTS
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SPECIFICATION (14 pp.); CLAIMS (5 pp.); ABSTRACT (1 p.); DRAWING (1 p.); PROVISIONAL APPLICATION COVER SHEET (1p. in triplicate); APPENDIX A (9 pp.); APPENDIX B (5 pp. [front & back]); CHECK IN THE AMOUNT OF $150.00 FOR FILING FEE; and POSTCARD (1 p.)

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METHOD TO TREAT FUNCTIONAL SOMATIC SYNDROMES AND FOR DIAGNOSING A PATIENT BASED ON A FUNCTIONAL SOMATIC SYNDROME SYMPTOM

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention generally relates to a method to treat a patient suffering from a functional somatic syndrome with an upper airway stabilizing technique during sleep. The present invention also relates to a method of diagnosing a patient as having a sleep disorder based on at least one symptom commonly associated with a functional somatic syndrome.

2. Description of the Related Art

[0002] Functional somatic syndromes (FSS) are defined as physical syndromes without an organic disease explanation, demonstrable structural changes, or established biochemical abnormalities. Thus, patients suffering from FSS are characterized more by symptoms, suffering, and disability than by consistently demonstrable tissue abnormalities. Examples of FSS include multiple chemical sensitivity, sick building syndrome, repetition stress injury, side effects of silicone breast implants, Gulf War syndrome, chronic whiplash, chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia.

[0003] The current standard for treating functional somatic syndromes is through the use of drugs, physical therapy, and/or psychotherapy, which are directed primarily at the FSS symptoms. These treatment techniques, however, each have disadvantages and have limited efficacy in treating the condition causing the symptoms. For example, drugs may not be tolerated by certain patients and often require long-term use. Physical therapy is time consuming, often painful, and is limited to those patients who have sufficient mobility to receive this form of treatment. Finally, many patients may be resistive to the use of psychotherapy, and

it is not clear whether it is effective for many patients. In addition, psychotherapy fails to address any underlying medical condition that the patient may have. All of these conventional treatments focus on treating only the symptoms of the FSS.

SUMMARY OF THE INVENTION

[0004] Accordingly, it is an object of the present invention to provide a method to treat a functional somatic syndrome (FSS) that overcomes the shortcomings of conventional treatment techniques. This object is achieved according to one embodiment of the present invention by providing a method to treat a FSS comprising the steps of: (1) identifying a patient as having a FSS or a symptom thereof, and treating such a patient with an airway stabilization technique. Suitable airway stabilization techniques include mechanical stabilization, for example using an oral appliance, and a positive pressure therapy, such as a continuous positive airway pressure (CPAP) therapy.

[0005] The method may further include determining whether the patient has an inspiratory flow limitation and classifying the patient as having an upper airway resistance syndrome (UARS) or obstructive sleep apnea/hypopnea (OSA/H) based on the inspiratory flow limitation determination. The method may further include observing alpha-delta sleep of a patient. The present inventor has determined that there may be symptomatic links between FSS, OSA/H, and UARS. Therefore, the present invention contemplates using an airway stabilization treatment, which is commonly used to treat UARS or OSA/H, to treat a FSS.

[0006] It is a further objective to provide a method of diagnosing a patient as having a sleep disorder comprising the steps of (1) determining whether a patient suffers from at least one symptom selected from the group comprising: sleep onset insomnia, headache, irritable bowel pain, alpha-delta sleep, and bruxism, and (2) diagnosing a patient having at least one of these

symptoms as having sleep-disordered breathing. The present invention further contemplates focusing the diagnosis based on whether the patient has alpha-delta sleep.

[0007] These and other objects, features and characteristics of the present invention, as well as the methods of operation and functions of the related elements of structure and the combination of parts and economies of manufacture, will become more apparent upon consideration of the following description and the appended claims with reference to the accompanying drawings, all of which form a part of this specification, wherein like reference numerals designate corresponding parts in the various figures. It is to be expressly understood, however, that the drawings are for the purpose of illustration and description only and are not intended as a definition of the limits of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Fig. 1 is a bar chart showing the percentage of UARS and OSA/H patients that exhibit eleven pre-selected symptoms.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS OF THE INVENTION

[0009] The present inventor observed that OSA/H and UARS patients both often present with signs/symptoms of snoring, fitful sleep, and daytime sleepiness/fatigue. However, as shown in Fig. 1, the inventor also found that UARS patients present more frequently with certain symptoms, such as sleep onset insomnia, headache, irritable bowel syndrome, alpha-delta sleep, bruxism, depression and other symptoms not identified in Fig. 1. The higher percentage of these particular symptoms may allow physicians to better diagnose UARS from OSA/H, but it should

be noted that these particular symptoms may be found in mild/moderate OSA/H patients and, with the exception of alpha-delta sleep, in moderate/severe OSA/H patients as well.

[0010] It has also been found that a polysomnogram may offer some clues to treating FSS, UARS, and OSA/H. While patients with UARS and OSA/H experience recurrent arousals from sleep, OSA/H patients demonstrate decreases of inspiratory flow to less than fifty percent of waking levels associated with oxyhemoglobin desaturation. Patients with UARS have less severe inspiratory flow limitation, such as a limitation of inspiratory flow of approximately one to fifty percent of waking levels, due to a less collapsible upper airway. There is also the more frequent presence of alpha-delta sleep, or the intrusion of waking alpha rhythm into deep, slow-wave sleep, in UARS patients versus mild to moderate OSA/H patients. No appreciable alpha-delta sleep was detected in moderate/severe OSA/H patients.

[0011] Another point of interest is that UARS and some OSA/H patients complain of ailments that are also found in patients diagnosed with FSS. FSS and UARS or OSA/H patients can both present with chronic fatigue, irritable bowel syndrome, a migraine headache, a tension headache, temporomandibular joint syndrome, sleep-onset insomnia, sleep maintenance insomnia, unrefreshing sleep, heartburn, abdominal pain, abdominal urgency, diarrhea, headaches, depression, and orthostatic syncope. Therefore, there are several common symptoms of both FSS and UARS and OSA/H. This has led to the determination that FSS patients can be treated with upper airway stabilizing methods and devices. Thus, the present invention contemplates identifying symptoms of a functional somatic syndrome (FSS) that are similar to symptoms of upper airway resistance syndrome (UARS) or obstructive sleep apnea/hypopnea (OSA/H) and then treating the FSS with an upper airway stabilizing device or method during sleep, such as those methods or devices used to treat OSA/H or UARS.

[0012] OSA/H and UARS treatments suitable for use in the present invention for treating FSS include, but are not limited to, devices that deliver positive pressure therapy and mechanical stabilization devices. Examples of devices that deliver a positive pressure therapy to a patient include the following:

1) a continuous positive airway pressure (CPAP) device that delivers a continuous flow of gas at a constant pressure;
2) a bi-level positive airway pressure support device in which the pressure of gas delivered to the patient varies with the patient's breathing cycle; and
3) an auto-titrating positive airway pressure device in which the pressure of the flow of breathing gas provided to the patient changes based on the detected conditions of the patient, such as whether the patient is snoring or experiencing an apnea, hypopnea or upper airway resistance.

[0013] An example of a CPAP device is the REMstar® and Solo® family of CPAP devices manufactured by Respironics, Inc. of Pittsburgh, PA. A bi-level pressure support system provides an inspiratory positive airway pressure (IPAP) that is greater than an expiratory positive airway pressure (EPAP), which the pressure is delivered during the patient's expiratory phase. Such a bi-level mode of pressure support is provided by the BiPAP® family of devices manufactured and distributed by Respironics, Inc. and is taught, for example, in U.S. Patent Nos. 5,148,802 to Sanders et al., 5,313,937 to Zdrojkowski et al., 5,433,193 to Sanders et al., 5,632,269 to Zdrojkowski et al., 5,803,065 to Zdrojkowski et al., and 6,029,664 to Zdrojkowski et al., the contents of each of which are incorporated by reference into the present invention.

[0014] An example of an auto-titrating device that adjusts the pressure delivered to the patient based on whether or not the patient is snoring is the Virtuoso® CPAP family of devices

manufactured and distributed by Respironics, Inc. This auto-titration pressure support mode is taught, for example, in U.S. Patent Nos. 5,203,343; 5,458,137 and 6,087,747 all to Axe et al., the contents of which are incorporated herein by reference. Examples of conventional auto-titration pressure support systems are disclosed in U.S. Patent Nos. 5,245,995 to Sullivan et al.; 5,259,373; 5,549,106, and 5,845,636 all to Gruenke et al.; 5,458,137 and 6,058,747 both to Axe et al.; 5,704,345; 6,029,665, and 6,138,675 all to Berthon-Jones; 5,645,053 to Remmers et al.; and 5,335,654, 5,490,502, 5,535,739, and 5,803,066 all to Rapoport et al.

[0015] Other modes of providing positive pressure support to a patient that is suitable for use in stabilizing a patient's airway include, for example, proportional assist ventilation (PAV®), which is a mode of pressure support in which the pressure of gas delivered to the patient varies with the patient's breathing effort to increase the comfort to the patient. U.S. Patent Nos. 5,044,362 and 5,107,830 both to Younes, the contents of which are incorporated herein by reference, teach a pressure support device capable of operating in a PAV® mode. In addition, proportional positive airway pressure (PPAP) devices deliver breathing gas to the patient based on the flow generated by the patient. U.S. Patent Nos. 5,535,738, 5,794,615, and 6,105,573 all to Estes et al., the contents of which are incorporated herein by reference, teach a pressure support device capable of operating in a PPAP mode.

[0016] Examples of mechanical devices that serve to stabilize the airway include the following:

1) an oral appliance that controls or adjusts a position of an anatomical feature of a patient, such a mandibular positing device, a soft pallet lifting device, and a tongue positing or advancement device;

2) a device that applies a negative pressure or a distending force to exterior of the patient, for example, in the neck region, to maintain the airway in an open condition; and

3) a stimulation device that applies a stimulating energy, such as an electrical or magnetic stimulation, to the patient to maintain the patency of the patient's airway.

[0017] An example of an oral appliance that controls a position of an anatomical feature of a patient from within the oral cavity to stabilize the patient's airway is disclosed in PCT Applicaiton No. PCT/US01/01874 (Pub. No. WO 01/52928). More specifically, this PCT application discloses airway stabilization techniques by controlling the position of the tongue, the soft palate, the mandible, or any combination thereof. Other patents that teach airway stabilization via an oral appliance that controls the position of a feature of a patient include U.S. Patent No. 3,132,647 to Corniello; 4,169,473 to Samelson; 4,196,724 to Wirt et al.; 4,676,240 to Garty; 4,901,737 to Toone; 5,056,534 to Wright; 5,154,184 to Alvarez; 5,373,859 to Forney; 5,409,017 to Lowe; 5,826,579 to Remmers et al.; 5,868,138 to Halstrom; 5,915,385 to Hakimi; 5,988,171 to Sohn et al.; and 6,092,523 to Belfer.

[0018] An example of a device that applies a negative pressure or a distending force to exterior of the patient is disclosed in U.S. Patent No. 5,343,878 to Scarberry et al. and 5,343,878 also to Scarberry et al. According to this technique, a distending force is applied to the external surface of the patient via, for example, a negative pressure or an adhesive, to pull open the patient's airway, thereby stabilizing it and preventing its collapse.

[0019] Examples of devices that apply an electrical stimulation, either internally or externally, to the patient to maintain the patency of the patient's airway is disclosed in U.S.

Patent Nos. 6,212,435 to Lattner et al.; 4,830,008 to Meer; 5,123,425 to Shannon et al.; 5,146,918 to Kallok et al.; 5,190,053 to Meer; 5,591,216 to Testerman et al.; and 5,522,862 to Testerman et al. An example of a device that applies magnetic stimulation to maintain the patency of the patient's airway is disclosed in published PCT Application No. PCT/US98/21864 (Pub. No. WO 99/20339). An example of a device that uses an implanted microstimulator is also disclosed in this PCT application, as well as in U.S. Patent No. 6,240,316 to Richmond et al.

[0020] It can be appreciated that the present invention contemplates using any airway stabilization technique, e.g., positive airway pressure support or mechanical airway support. In addition, multiple airway stabilization techniques can be used in combination, such as the combination of a CPAP therapy and a tongue positing device, to treat the patient. The present invention is not intended to be limited to the airway stabilization techniques given above, nor is this listing intended to be exhaustive. In addition, as new airway stabilization techniques are developed, including surgical and pharmacological solutions, they may be equally suitable for use in the present method.

[0021] The following example illustrates how UARS, OSA/H and FSS may be related from a treatment standpoint. In addition, attached as Appendix A, is an article entitled, "The Symptoms and Signs of Upper Airway Resistance Syndrome" and attached as Appendix B, is an article entitled, "Upper Airway Collapsibility During Sleep in Upper Airway Resistance Syndrome", both of which are herein incorporated by reference in their entirety and both of which are co-authored by the present inventor. The former article discloses the details of the following example as well as explains the relationship between FSS, UARS and OSA/H. The latter article is provided to explain and better understand UARS and OSA/H.

EXAMPLE

[0022] The present inventor conducted a study in which seventy-five patients with UARS and OSA/H were selected for the study. Twenty-five UARS patients had an apnea hypopnea index (AHI) of less than 10/h. Twenty-five patients had mild to moderate OSA/H and an AHI of greater than or equal to 10/h but less than 40/h. Twenty-five patients had moderate to severe OSA/H and an AHI greater than or equal to 40/h.

[0023] Patients underwent comprehensive medical histories, physical examinations, and full-night polysomnography. The diagnosis of UARS included quantitative measurement of inspiratory airflow and inspiratory effort with demonstration of inspiratory flow limitation during sleep. The percentage of women among the patients with sleep-disordered breathing ($p=0.001$) and the prevalence of sleep-onset insomnia ($p=0.04$), headaches ($p=0.01$), irritable bowel syndrome ($p=0.01$), and alpha-delta sleep ($p=0.01$) was correlated with decreasing AHI. The diagnostic methods used to established the diagnosis of UARS and OSA/H and the methods used to compare the symptoms between the three groups of sleep-disordered breathing patients follow.

[0024] All of the patients referred were included in the survey because of a clinical suspicion of sleep-disordered breathing. Patients with fibromyalgia referred for evaluation of sleep-disordered breathing were excluded because they would be expected to have the symptoms of the FSS. On scheduling a sleep consultation, each patient received a detailed general medical history questionnaire and a sleep-related symptom questionnaire to complete and bring to the consultation. The sleep consultation was performed by a physician with credentials in both internal medicine and sleep medicine, and included a general medical and sleep-related history and physical examination.

[0025] Polysomnography was performed between the hours of 10:00 PM and 6:00 AM. Sleep stages were monitored using surface EEG activity of the central and occipital regions, submental surface electromyographic activity, and left and right electro-oculographic activity. Leg movement was detected using surface electromyographic activity of the right and left tibialis anterior muscle. Airflow at the nose and mouth was monitored with a thermocouple. Thoracoabdominal movement was monitored with piezoelectric belts. Oxyhemoglobin saturation was monitored at the finger using a pulse oximeter. A continuous ECG monitored heart rate and rhythm. All of the data were converted from analog to digital and stored on a computer for analysis by a board-certified sleep physician.

[0026] Respiratory events were defined as any combination of apnea and hypopnea lasting at least 10 seconds and associated with an arousal. Apnea was defined as a decrease of inspiratory airflow to less than 20% of waking levels, and hypopnea was defined as a decrease in inspiratory airflow to less than 50% of waking levels. The clinical diagnosis of OSA/H was established by an apnea/hypopnea index (AHI) of at least ten events per hour of sleep. Patients presenting with symptoms of sleep-disordered breathing, but with an AHI of less than 10/h received a presumptive diagnosis of UARS. The diagnosis of UARS was confirmed after further evaluation with a diagnostic nasal continuous positive airway pressure study.

[0027] All patients with a presumptive diagnosis of UARS underwent a nasal CPAP study to demonstrate inspiratory airflow limitation during non-rapid eye movement (NREM) sleep (confirming UARS) and to determine a therapeutic level of nasal CPAP.

[0028] During the nasal CPAP study, each patient slept wearing a nasal CPAP mask available commercially from Respironics, Inc., Murrysville, PA. The mask was attached via a breathing circuit and a bi-directional valve to a pressure support system capable of administering

a positive airway pressure, such as a CPAP device, and to a source of negative pressure, such as a modified REMstar® brand CPAP unit also commercially available from Respironics, Inc. Using the dual pressure sources, the present inventor was able to vary the mask pressure between -20 cm H_2O and 20 cm H_2O. The monitoring of sleep stages, leg movements, heart rhythm, and oxyhemoglobin saturation during the nasal CPAP study was the same as for polysomnography.

[0029] Nasal airflow was measured with a heated pneumotachograph, such as a Model 3813, commercially available from Hans Rudolph, Kansas City, MO and transducer Model MP45-14-871, S/N 45534, commercially available from Validyne Engineering, Northridge, CA interposed between the bi-directional valve and the nasal mask. Inspiratory effort was measured as esophageal pressure using a saline solution-filled infant feeding tube with side ports at its distal 1 cm attached to a disposable pressure transducer, such as a Model 00-041576504A, commercially available from Maxxim, Athens, TX. The distal 1 cm of the feeding tube was positioned in the middle third of the esophagus. Nasal mask pressure (Pmask) was monitored directly from a port in the mask using a differential pressure transducer (Model 23ID, Spectramed, Oxnard, CA) referenced to atmosphere.

[0030] To demonstrate sleep related inspiratory flow limitation, Pmask is set at atmospheric pressure (between 1 cm H_2O and $-$ 1 cm H_2O). Inspiratory flow limitation is considered to occur when inspiratory airflow becomes maximal despite an increasing driving pressure for airflow (a decreasing esophageal pressure). The combination of excessive daytime sleepiness/fatigue, an AHI less than 10/h, and evidence of inspiratory flow limitation during NREM sleep with Pmask at atmospheric pressure establishes the diagnosis of UARS.

[0031] The following symptoms/signs associated with FSS, as defined below, were investigated during the study:

- Sleep-onset insomnia: a subjective inability to fall asleep in less than 30 min.;
- Headaches: a diagnosis of migraine headaches established by a physician or the occurrence of any headache (other than a morning headache on awakening) at least once weekly;
- Rhinitis: any two of the following: the presence of chronic nasal stuffiness, the presence of chronic postnasal drip, the presence of chronic or seasonal nasal allergies;
- Gastroesophageal reflux: a diagnosis of gastroesophageal reflux established by a physician or the presence of heartburn (every week) for which the patient regularly receives antacids or histamine type-2 blocking agents;
- Asthma: a diagnosis of asthma established by a physician or the presence of wheezing during our physical examination of a nonsmoker;
- Depression: the diagnosis of depression by a psychiatrist or psychologist, or the diagnosis by an internist associated with the prescription of antidepressant medication;
- Hypothyroidism: diagnosed by a physician and treated with thyroid replacement;
- Bruxism: the observation by a bed partner of "tooth grinding" or the observation by a dentist of the characteristic of tooth wear;
- Alpha-delta sleep: a polysomnographic EEG pattern characterized by the superimposition of alpha rhythm on the delta rhythm of slow-wave sleep. The presence of alpha-delta sleep was determined by a board-certified sleep physician evaluating the full-night polysomnogram (first-sleep study);
- IBS: a diagnosis of IBS established by a physician or the regular occurrence of two of the following symptoms: diarrhea alternating with constipation, abdominal pain/urgency, or gaseous bloating;

- Orthostatic syncope: the frequent experiencing of "light headedness" (not a sensation of "spinning") on arising from a seated or supine position in a patient not being treated with diuretics or antihypertensives.

[0032] Only current symptoms/signs were considered present. Symptoms/signs that had been experienced prior to our consultation, but that did not continue, were considered absent.

[0033] To ensure a broad range of sleep-disordered breathing severity in our patients, we collected 25 consecutive patients at each of three levels of severity of AHI UARS (AHI less than 10/r), mild-to-moderate OSA/H (AHI less than or equal to 10 to less than 40/h), and moderate-to-severe OSA/H (AHI less than or equal to 40/h). We reviewed each patient's questionnaires, history, physical examination, and polysomnogram to abstract the needed information. Whenever our review determined that information was missing, the physician who performed the consultation obtained the missing information during the next clinical contact (usually within one month of polysomnography). The designation of symptoms/signs as "present" or "absent" according to the criteria listed above was done by individuals blinded to the severity of the patient's sleep-disordered breathing.

[0034] Demographic differences between groups were tested on continuous outcomes with one-way analysis of variance. Differences on categorical outcomes were tested with the X2 statistic. The correlation between the prevalence of the specified symptoms/signs and decreasing severity of AHI grouping was tested nonparametrically with the Cochran-Mantel-Haonszel (CMH) test of zero correlation. A statistically significant p value would indicate a significant positive or negative correlation between prevalence of a symptom/sign and decreasing severity of AHI group.

[0035] As shown in the example above, and particularly Fig. 1, patients with sleeping disorders experience a wide variety of symptoms, and these symptoms overlap with symptoms of FSS listed above. Therefore, treatment of FSS symptoms with UARS and OSA/H treatment methods may alleviate the symptoms or cause of the FSS. Moreover, as further evidenced by Fig. 1, certain symptoms associated with FSS appear more frequently in patients having UARS, which could lead to more exact diagnosis. Finally, the absence of alpha-delta sleep can be used to diagnose moderate to severe OSA/H or to further focus on a UARS or mild/moderate OSA/H diagnosis.

[0036] Although the invention has been described in detail for the purpose of illustration based on what is currently considered to be the most practical and preferred embodiments, it is to be understood that such detail is solely for that purpose and that the invention is not limited to the disclosed embodiments, but, on the contrary, is intended to cover modifications and equivalent arrangements that are within the spirit and scope of the appended claims.

We Claim:

1. A method of treating a functional somatic syndrome comprising the steps of:

identifying a patient as having a functional somatic syndrome; and

treating such a patient with an airway stabilization technique.

2. The method as claimed in claim 1, wherein treating such a patient with an airway stabilization technique comprises stabilizing the airway with a mechanical stabilization.

3. The method as claimed in claim 2, wherein the mechanical stabilization is selected from the group consisting of:

an oral appliance adapted to control a position of an anatomical feature of a patient;

a tissue distending device adapted to located externally and coupled to such a patient so as to distend tissue associated with such a patient's airway; or

a stimulation device adapted to apply a stimulating energy to a patient.

4. The method as claimed in claim 1, wherein treating such a patient with an airway stabilization technique comprises stabilizing the airway with a positive pressure therapy.

5. The method as claimed in claim 4, wherein the positive pressure therapy is selected from the group consisting of: a continuous positive airway pressure, a bi-level positive airway pressure, or an auto-titrating positive airway pressure.

6. The method as claimed in claim 1, wherein identifying a patient as having a functional somatic syndrome includes identifying a symptom of the functional somatic syndrome, wherein the symptom is selected from the group comprising: chronic fatigue, fibromyalgia, irritable bowel, a migraine headache, a tension headache, temporomandibular joint pain, premenstrual pain, sleep-onset insomnia, maintenance insomnia, unrefreshed sleep, EEG evidence of sleep fragmentation, bruxism, muscle pain, muscle tenderness, heartburn, abdominal pain, abdominal urgency, diarrhea, headaches, depression, and orthostatic syncope.

7. The method as claimed in claim 1, further comprising the step of monitoring such a patient for an inspiratory flow limitation.

8. The method as claimed in claim 7, further comprising the step of categorizing a patient who has an inspiratory flow limitation of approximately one to fifty percent of a wake level as an upper airway resistance syndrome patient.

9. The method as claimed in claim 7, further comprising the step of categorizing a patient who has an inspiratory flow limitation of approximately fifty-one to one-hundred percent of a wake level as an obstructive sleep apnea patient.

10. The method as claimed in claim 1, further comprising observing alpha-delta sleep of such a patient.

11. The method as claimed in claim 1, wherein the functional somatic syndrome is selected from the group consisting of: chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, a migraine headache, a tension headache, temporomandibular joint syndrome, Gulf War syndrome, premenstrual syndrome, sleep-onset insomnia, and maintenance insomnia.

12. A method of treating a functional somatic syndrome comprising the steps of:

identifying a patient as having a symptom of functional somatic syndrome; and

treating such a patient with an airway stabilization technique.

13. The method as claimed in claim 12, wherein treating such a patient with an airway stabilization technique comprises stabilizing the airway with a mechanical stabilization.

14. The method as claimed in claim 13, wherein the mechanical stabilization is selected from the group consisting of:

an oral appliance adapted to control a position of an anatomical feature of a patient;

a tissue distending device adapted to located externally and coupled to such a patient so as to distend tissue associated with such a patient's airway; or

a stimulation device adapted to apply a stimulating energy to a patient.

15. The method as claimed in claim 12, wherein treating such a patient with an airway stabilization technique comprises stabilizing the airway with a positive pressure therapy.

16. The method as claimed in claim 15, wherein the positive pressure therapy is selected from the group consisting of: a continuous positive airway pressure, a bi-level positive airway pressure, or an auto-titrating positive airway pressure.

17. The method as claimed in claim 1, wherein the symptom of the functional somatic syndrome is selected from the group comprising: chronic fatigue, fibromyalgia, irritable bowel, a migraine headache, a tension headache, temporomandibular joint pain, premenstrual pain, sleep-onset insomnia, maintenance insomnia, unrefreshed sleep, EEG evidence of sleep fragmentation, bruxism, muscle pain, muscle tenderness, heartburn, abdominal pain, abdominal urgency, diarrhea, headaches, depression, and orthostatic syncope.

18. A method to diagnose a sleep disorder comprising the steps of:

a) determining whether a patient suffers from at least one symptom selected from the group comprising: sleep-onset insomnia, headache, irritable bowel pain, alpha-delta sleep, and bruxism; and

b) diagnosing a patient having at least one of the symptoms recited in step a) as having sleep-disordered breathing.

19. The method as claimed in claim 18, further comprising the step of diagnosing the patient as a moderate to severe OSA/H patient if alpha-delta sleep is not present.

20. The method as claimed in claim 18, further comprising the step of diagnosing the patient as a UARS or mild to moderate OSA/H patient if alpha-delta sleep is present.

ABSTRACT OF THE DISCLOSURE

A method of treating a functional somatic syndrome that includes identifying a patient as having a functional somatic syndrome or a symptom thereof and treating such a patient with an airway stabilization technique. Suitable airway stabilization techniques include positive pressure therapies, such as a CPAP treatment and a mechanical airway stabilization device. The present invention also is directed to a method of diagnosing a sleep disorder that includes determining whether a patient suffers sleep-onset insomnia, headache, irritable bowel pain, alpha-delta sleep, or bruxism, and diagnosing a patient having at least one of these symptoms as having sleep-disordered breathing.

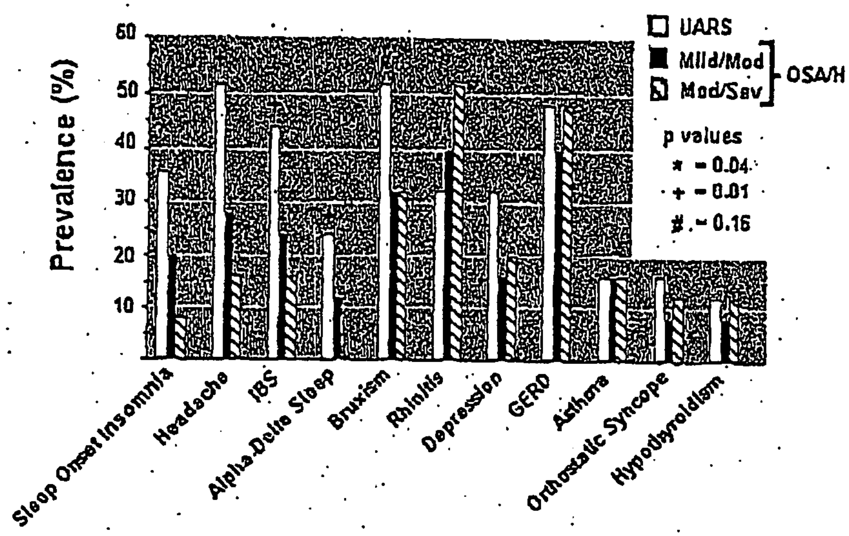
Prevalence (%)
60
50
40
30
20
10
UARS
Mild/Mod
Mod/Sev
OSA/H
p values
* = 0.04
+ = 0.01
# = 0.16
Sleep Onset Insomnia
Headache
IBS
Alpha-Delta Sleep
Bruxism
Rhinitis
Depression
GERD
Asthma
Orthostatic Syncope
Hypothyroidism

FIG. 1

APPENDIX A

The Symptoms and Signs of Upper Airway Resistance Syndrome*

A Link to the Functional Somatic Syndromes

Avram R. Gold, MD; Francis Dipalo, DO; Morris S. Gold, DSc; and Daniel O'Hearn, MD

Study objectives: The functional somatic syndromes are associated with a variety of symptoms/signs of uncertain etiology. We determined the prevalence of several of those symptoms/signs in patients with sleep-disordered breathing and examined the relationship between the prevalence of the symptoms/signs and the severity of sleep-disordered breathing.
Design: A descriptive study without intervention.
Setting: A university sleep-disorders center located in a suburban setting.
Patients or participants: Three groups of 25 consecutively collected patients with sleep-disordered breathing. Groups varied in their apnea hypopnea indexes (AHIs) as follows: upper airway resistance syndrome (UARS) [AHI < 10/h), mild-to-moderate obstructive sleep apnea/hypopnea (OSA/H) [AHI ≥ 10 to < 40/h), and moderate-to-severe OSA/H (AHI ≥ 40/h).
Measurements and results: Patients underwent comprehensive medical histories, physical examinations, and full-night polysomnography. The diagnosis of UARS included quantitative measurement of inspiratory airflow and inspiratory effort with demonstration of inspiratory flow limitation. The percentage of women among the patients with sleep-disordered breathing ($p = 0.001$) and the prevalence of sleep-onset insomnia ($p = 0.04$), headaches ($p = 0.01$), irritable bowel syndrome ($p = 0.01$), and alpha-delta sleep ($p = 0.01$) was correlated with decreasing severity of AHI group.
Conclusions: We conclude that in patients with UARS, mild-to-moderate OSA/H and moderate-to-severe OSA/H differ in their presenting symptoms/signs. The symptoms/signs of UARS closely resemble those of the functional somatic syndromes. *(CHEST 2002; 122:1–??)*

Key words: alpha-delta sleep; bruxism; chronic fatigue syndrome; fibromyalgia; functional somatic syndromes; irritable bowel syndrome; sleep-disordered breathing; temporomandibular joint syndrome; upper airway resistance syndrome

Abbreviations: AHI = apnea/hypopnea index; BMI = body mass index; CMH = Cochran-Mantel-Haenszel; CPAP = continuous positive airway pressure; IBS = irritable bowel syndrome; NREM = non-rapid eye movement; OSA/H = obstructive sleep apnea/hypopnea; Pmask = nasal mask pressure; UARS = upper airway resistance syndrome

During the past decade, physicians treating sleep disorders have experienced a broadening of the spectrum of sleep-disordered breathing. In addition, to the obstructive sleep apnea/hypopnea syndrome (OSA/H), many researchers and clinicians now recognize the upper airway resistance syndrome (UARS).[1] Both OSA/H and UARS often present with the signs/symptoms of snoring, fitful sleep, and daytime sleepiness/fatigue. The chief difference between the two syndromes can be found in the airflow channel of the polysomnogram. While patients with both syndromes experience recurrent arousals from sleep, OSA/H patients demonstrate decreases of inspiratory flow to < 50% of waking levels associated with oxyhemoglobin desaturation, while patients with UARS have less severe inspiratory flow limitation.[1,2] In a previous study,[2] we demonstrated that the less severe inspiratory flow limitation of patients with UARS during sleep is associated with a less collapsible upper airway.

When viewed from the perspective of upper airway physiology, patients with UARS and patients with OSA/H are similar, differing only in the severity

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of their upper airway collapsibility during sleep. In a recent editorial,[3] however, Guilleminault and Chowdhuri[3] suggested that patients with UARS are younger and more often female than patients with OSA/H and complain more frequently of sleep-onset insomnia and fatigue. In addition, Guilleminault and associates[4] found a greater prevalence of orthostatic intolerance in patients with UARS than in patients with OSA/H. In our previous study,[2] we observed similar age and gender differences between patients with UARS and patients with OSA/H. Furthermore, it has been our impression that patients with UARS who we see in our practice present with sleep-onset insomnia, headaches, gastroesophageal reflux, depression, bruxism (grinding of teeth), symptoms of rhinitis, hypothyroidism, and asthma more frequently than do patients with OSA/H. These observations have led us to hypothesize that patients with UARS have a different clinical presentation from patients with OSA/H.

In addition to the differences we have observed between patients with UARS and patients with OSA/H in demographics and symptoms/signs, we have observed a remarkable feature in the polysomnograms of several of our patients with UARS: the EEG finding of alpha-delta sleep.[5] Alpha-delta sleep, the intrusion of waking alpha rhythm into deep, slow-wave sleep, is not known to be a feature in patients with OSA/H. Rather, it has been observed in a variety of syndromes associated with chronic fatigue.[6–8] The functional somatic syndromes[9–11] include chronic fatigue syndrome,[12] fibromyalgia,[13] irritable bowel syndrome (IBS),[14,15] migraine/tension headaches,[16] and temporomandibular joint syndrome.[7,17,18] In addition to a common symptom of excessive sleepiness/fatigue, these syndromes feature the following symptoms/signs: sleep-onset and maintenance insomnia, unrefreshing sleep, EEG evidence of sleep fragmentation, bruxism, muscle pain and tenderness, heartburn, abdominal pain/urgency, diarrhea, headaches, depression, and orthostatic syncope.[18,20] Thus, the symptoms/signs we have observed in patients with UARS appear to overlap substantially with the symptoms/signs of the functional somatic syndromes.

Combining the findings of previous investigators and our observations above, we hypothesized that patients with UARS have a clinical presentation that differs from that of patients with OSA/H and resembles the clinical presentation of the functional somatic syndromes. To test this hypothesis, we have determined the prevalence of a variety of symptoms/signs in consecutively evaluated patients with sleep-disordered breathing.

Materials and Methods

The study is a prospective examination of the prevalence of a variety of symptoms/signs in 75 patients with UARS and OSA/H (25 consecutive patients with sleep-disordered breathing at each of three levels of severity). All of the patients were referred to the SUNY Sleep Disorders Center–Medicine because of a clinical suspicion of sleep-disordered breathing. Patients with fibromyalgia referred for evaluation of sleep-disordered breathing[21] were excluded because they would be expected to have the symptoms of the functional somatic syndromes. This study was approved by the Institutional Review Board of SUNY at Stony Brook School of Medicine.

Evaluation of Sleep-Disordered Breathing

Consultation: On scheduling a sleep consultation, each patient received a detailed general medical history questionnaire and a sleep-related symptoms questionnaire to complete and bring to the consultation. The sleep consultation was performed by a physician with credentials in both internal medicine and sleep medicine, and included a general medical and sleep-related history and physical examination.

Full-Night Polysomnography: Polysomnography was performed between the hours of 10 PM and 6 AM. Sleep stages were monitored using surface EEG activity of the central and occipital regions, submental surface electromyographic activity, and left and right electro-oculographic activity. Leg movement was detected using surface electromyographic activity of the right and left tibialis anterior muscle. Airflow at the nose and mouth was monitored with a thermocouple. Thoracoabdominal movement was monitored with piezoelectric belts. Oxyhemoglobin saturation was monitored at the finger using a pulse oximeter. A continuous ECG monitored heart rate and rhythm. All of the data were converted from analog to digital and stored on a computer for analysis by a board-certified sleep physician.

Respiratory events were defined as any combination of apnea and hypopnea lasting at least 10 s and associated with an arousal. Apnea was defined as a decrease of inspiratory airflow to < 20% of waking levels, and hypopnea was defined as a decrease in inspiratory airflow to < 50% of waking levels. The clinical diagnosis of OSA/H was established by an apnea/hypopnea index (AHI) of at least 10 events per hour of sleep. Patients presenting with symptoms of sleep-disordered breathing, but with an AHI of < 10/h received a presumptive diagnosis of UARS. The diagnosis of UARS was confirmed after further evaluation with a diagnostic nasal continuous positive airway pressure (CPAP) study.

Nasal CPAP Study: All patients with a presumptive diagnosis of UARS underwent a nasal CPAP study to demonstrate inspiratory airflow limitation during non-rapid eye movement (NREM) sleep (confirming UARS) and to determine a therapeutic level of nasal CPAP.

During the nasal CPAP study, each patient slept wearing a nasal CPAP mask (Respironics; Murrysville, PA). The mask was attached via a breathing circuit and a bi-directional valve to a source of CPAP and to a source of negative pressure (a modified Rem-Star unit; Respironics). Using the dual pressure sources, we were able to vary the mask pressure between − 20 cm H_2O and 20 cm H_2O. The monitoring of sleep stages, leg movements, heart rhythm, and oxyhemoglobin saturation during the nasal CPAP study was the same as for polysomnography. Nasal airflow was measured with a heated pneumotachograph (model 3813; Hans Rudolph; Kansas City, MO) and transducer (model MP45–14-871 S/N 45534; Validyne Engineering; Northridge, CA) interposed between the bi-directional valve and the nasal mask. Inspiratory effort was measured as esophageal pressure using a saline solution-filled infant feeding tube with side ports at its

distal 1 cm attached to a disposable pressure transducer (model 00-041576504A. Maxxim. Athens, TX). The distal 1 cm of the feeding tube was positioned in the middle third of the esophagus. Nasal mask pressure (Pmask) was monitored directly from a port in the mask using a differential pressure transducer (model 23ID; Spectramed; Oxnard, CA) referenced to atmosphere.

Our methods for evaluating upper airway pressure/flow relationships have been described previously.[3] To demonstrate sleep-related inspiratory flow limitation, Pmask is set at atmospheric pressure (between 1 cm H_2O and − 1 cm H_2O). Inspiratory flow limitation is considered to occur when inspiratory airflow becomes maximal despite an increasing driving pressure for airflow (a decreasing esophageal pressure).

Because our laboratory does not place an esophageal catheter for every clinical polysomnogram, we cannot establish the diagnosis of UARS by demonstrating respiratory effort-related arousals during full-night polysomnography.[2] In our laboratory, the combination of excessive daytime sleepiness/fatigue, an AHI < 10/h, and evidence of inspiratory flow limitation during NREM sleep with Pmask at atmospheric pressure establishes the diagnosis of UARS.

Symptoms and Signs: We chose and defined the following symptoms/signs to investigate:

1. Sleep-onset insomnia: a subjective inability to fall asleep in < 30 min.
2. Headaches: a diagnosis of migraine headaches established by a physician or the occurrence of any headache (other than a morning headache on awakening) at least once weekly.
3. Rhinitis: any two of the following: the chronic presence of nasal stuffiness, the chronic presence of postnasal drip, of chronic or seasonal nasal allergies.
4. Gastroesophageal reflux: a diagnosis of gastroesophageal reflux established by a physician or the presence of heartburn (every week) for which the patient regularly receives antacids or histamine type-2 blocking agents.
5. Asthma: a diagnosis of asthma established by a physician or the presence of wheezing during our physical examination of a nonsmoker.
6. Depression: The diagnosis of depression by a psychiatrist or psychologist, or the diagnosis by an internist associated with the prescription of antidepressant medication.
7. Hypothyroidism: diagnosed by a physician and treated with thyroid replacement.
8. Bruxism: the observation by a bed partner of "tooth grinding" or the observation by a dentist of the characteristic tooth wear.
9. Alpha-delta sleep: a polysomnographic EEG pattern characterized by the superimposition of alpha rhythm on the delta rhythm of slow-wave sleep (Fig 1). The presence of alpha-delta sleep was determined by a board-certified sleep physician evaluating the full-night polysomnogram (first sleep study).
10. IBS: a diagnosis of IBS established by a physician or the regular occurrence of two of the following symptoms: diarrhea alternating with constipation, abdominal pain/urgency, or gaseous bloating.
11. Orthostatic syncope: the frequent experiencing of "light headedness" (not a sensation of "spinning") on arising from a seated or supine position in a patient not being treated with diuretics or antihypertensives.

We chose the first nine symptoms/signs because our clinical experience suggested that their prevalence would be greater in patients with UARS than in patients with OSA/H. We included the last two symptoms/signs because they have been observed in the functional somatic syndromes. We had not previously screened our patients with sleep-disordered breathing for symptoms of either IBS or orthostatic syncope. Only current symptoms/signs were considered present. Symptoms/signs that had been experienced prior to our consultation, but that did not continue, were considered absent.

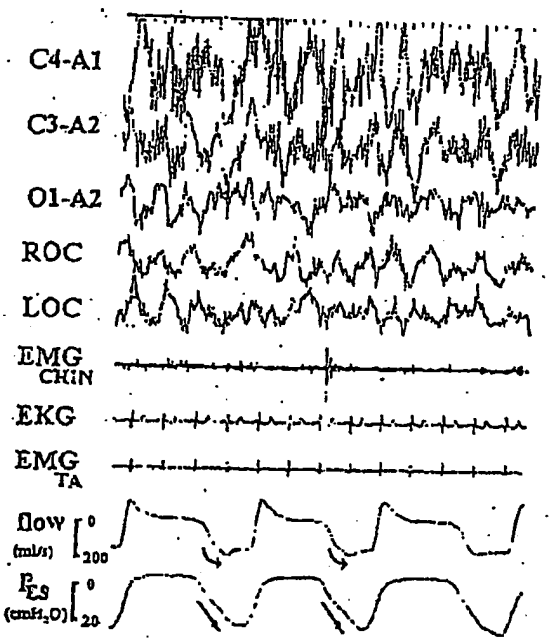

FIGURE 1. Alpha-delta sleep in a 53-year-old woman with snoring, severe sleepiness, an AHI of 0/h, and an arousal frequency of 29/h. The central EEG channels (C4-A1 and C3-A2) demonstrate low-frequency (< 2 cycles per second), high-amplitude (> 75 μV) delta waves with superimposed 7 to 11 cycle per second α waves characteristic of alpha-delta sleep. The airflow channel (flow) demonstrates a plateau of inspiratory airflow (downgoing curved arrow) despite a continuing increase in the pressure driving airflow, the decreasing intrathoracic pressure (P_{ES}; downgoing arrow), characterizing inspiratory flow limitation. ROC/LOC are right and left electro-oculograms; EMG$_{CHIN}$/EMG$_{TA}$ are surface electromyograms of the chin and tibialis anterior muscle, respectively.

Experimental Design: To ensure a broad range of sleep-disordered breathing severity in our patients, we collected 25 consecutive patients at each of three levels of severity of AHI: UARS (AHI < 10/h), mild-to-moderate OSA/H (AHI ≥ 10 to < 40/h), and moderate-to-severe OSA/H (AHI ≥ 40/h). We reviewed each patient's questionnaires, history, physical examination, and polysomnogram to abstract the needed information. Whenever our review determined that information was missing, the physician who performed the consultation obtained the missing information during the next clinical contact (usually within 1 month of polysomnography). The designation of symptoms/signs as "present" or "absent" according to the criteria listed above was done by individuals blinded to the severity of the patient's sleep-disordered breathing.

Statistical Analysis: Demographic differences between groups were tested on continuous outcomes with one-way analysis of variance. Differences on categorical outcomes were tested with the χ^2 statistic. The correlation between the prevalence of the specified symptoms/signs and decreasing severity of AHI group-

ing was tested nonparametrically with the Cochran-Mantel-Haenszel (CMH) test of zero correlation. A statistically significant p value would indicate a significant positive or negative correlation between prevalence of a symptom/sign and decreasing severity of AHI group.

Results

The anthropometric and AHI data of our three groups of patients with sleep-disordered breathing are shown in Table 1. The patients with UARS were significantly younger than the patients with mild-to-moderate OSA/H ($p = 0.036$), but were not significantly younger than the patients with moderate-to-severe OSA/H. The patients with UARS had a significantly lower body mass index (BMI) than either group of patients with OSA/H ($p < 0.02$ for each comparison). Female patients constituted a significantly larger portion of the UARS group than of either OSA/H group ($p < 0.02$ for each comparison), with the prevalence of women among the patients progressively decreasing as the severity of AHI group increased ($p = 0.0005$, CMH test of zero correlation).

The sleep-related symptoms of our 75 patients are shown in Table 2. Nearly all of our patients had complaints of both sleepiness/fatigue and snoring. The three patients with UARS who did not have a history of snoring presented with sleepiness/fatigue and fitful, restless sleep. The two patients with mild-to-moderate OSA/H who did not complain of sleepiness/fatigue both had histories of snoring and witnessed apnea.

The relationship between the decreasing severity of AHI group and the prevalence of symptoms/signs of sleep-disordered breathing is demonstrated in Figure 2. There was a significant correlation between decreasing severity of AHI group and the prevalence of sleep-onset insomnia ($p = 0.04$), headache ($p = 0.01$), IBS ($p = 0.01$), and alpha-delta sleep ($p = 0.01$). Nonsignificant trends were present for the prevalence of bruxism ($p = 0.16$) and rhinitis ($p = 0.16$). Unlike the symptoms/signs that increased in prevalence with decreasing severity of AHI, the prevalence of rhinitis tended to decrease as severity of AHI decreased. There was no significant correlation between the prevalence of depression, GERD, asthma, hypothyroidism, or orthostatic syncope and the severity of AHI.

Table 1—*Anthropometric and AHI Data**

Variables	UARS	Mild-to-Moderate OSA/H	Moderate-to-Severe OSA/H
Age, yr	43 (15)†	52 (13)	48 (14)
BMI	29.9 (6)‡	35.6 (9)	38.4 (8)
Male/female gender	13/121	5/20	2/23
AHI, events/h	1.5 (3.3)	25.1 (10.2)	68.8 (17.4)

*Data are presented as mean (SD) or No.
†$p = 0.036$ vs mild-to-moderate OSA/H group.
‡$p < 0.02$ vs both OSA/H groups.

Table 2—*Sleep-Related Symptoms**

Variables	UARS	Mild-to-Moderate OSA/H	Moderate-to-Severe OSA/H
Sleepiness/fatigue	25 (100)	23 (92)	25 (100)
Snoring	22 (88)	25 (100)	25 (100)
Witnessed apnea	9 (36)	16 (64)	21 (84)
Fitful, restless sleep	16 (64)	17 (68)	16 (64)

*Data are presented as No. (% of group).

Alpha-delta sleep was present in six of our patients with UARS (8.9 ± 8.5% of total sleep time), in three of our patients with mild-to-moderate OSA/H (13.7 ± 7.4% of total sleep time), and in none of our patients with moderate-to-severe OSA/H. In patients with alpha-delta sleep, the finding was present in all slow-wave sleep observed during polysomnography. Furthermore, each patient with alpha-delta sleep during full-night polysomnography also had the finding during the CPAP study. Each patient without alpha-delta sleep during polysomnography did not display alpha-delta sleep during the CPAP study.

To evaluate whether the symptoms/signs whose prevalence were greatest in patients with UARS were widely distributed among those patients, or whether they were clustered in a small group of patients with numerous symptoms/signs, we chose five symptoms/signs that tended to be most prevalent in patients with UARS (sleep-onset insomnia, headache, IBS, alpha-delta sleep, and bruxism) and counted the frequency of these symptoms/signs in each patient with sleep-disordered breathing (Fig 3). We found that the five symptoms/signs tended to be widely distributed among patients with UARS. More than 96% of the patients with UARS had at least one symptom/sign, with 72% having from two to four symptoms/signs. Despite their decreased prevalence, the symptoms/signs were also widely distributed among patients with OSA/H, with 64% having at least one symptom/sign. Thus, the symptoms/signs that tended to be more prevalent in patients with UARS were broadly distributed among patients with sleep-disordered breathing and not just clustered in a small subset of patients with numerous symptoms/signs.

Because the functional somatic syndromes have a predilection for female subjects,[13] and the percent-

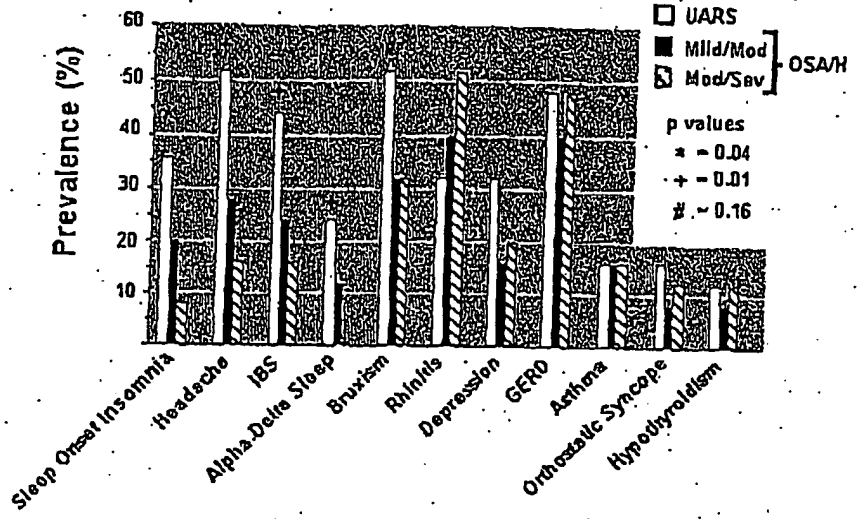

FIGURE 2. Prevalence of the various symptoms/signs in our patients with sleep-disordered breathing. The prevalence of sleep-onset insomnia, headache, IBS, and alpha-delta sleep increased with decreasing severity of AHI group to a statistically significant degree. Mod = moderate; Sev = severe.

age of women among our patients with sleep-disordered breathing increased with decreasing severity of AHI group, it could be argued that the differences observed in the prevalence of symptoms/signs between severity of AHI groups may have resulted from the gender differences between groups.[23] To investigate whether the increased prevalence of women among our patients with UARS accounted for the significantly higher prevalence of some symptoms/signs in the same group, we examined the prevalence of those symptoms/signs in our patients with sleep-disordered breathing as a func-

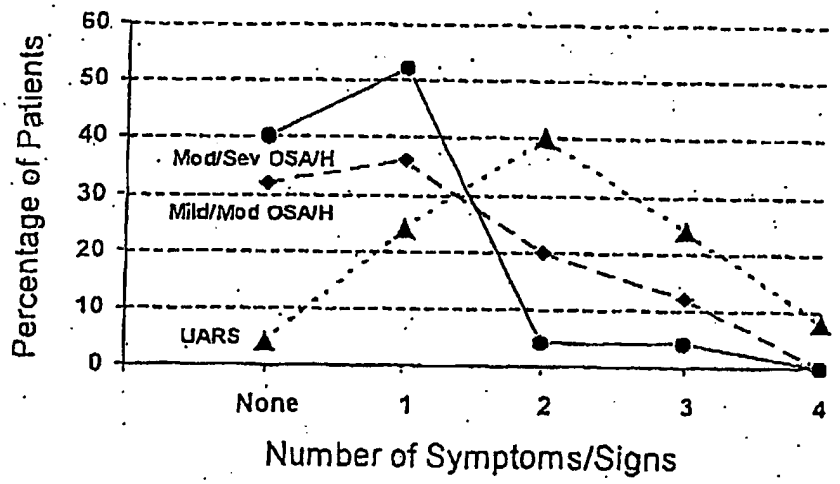

FIGURE 3. For the five symptoms/signs whose prevalence differed between groups (sleep-onset insomnia, headache, IBS, alpha-delta sleep, and bruxism), this graph illustrates the clustering of those symptoms in individual patients. The signs and symptoms were widely distributed among patients with UARS (dotted line with triangles), patients with mild-to-moderate OSA/H (dashed line with diamonds), and patients with moderate-to-severe OSA/H (solid line with circles). See Figure 2 for expansion of abbreviations.

tion of gender using the CMH test of zero correlation controlled for gender (Table 3). We found that the significant correlation between decreasing severity of AHI group and the prevalence of sleep-onset insomnia, headache, and alpha-delta sleep in Figure 2 remained apparent. The correlation became weakened for IBS (p value increased from 0.01 to 0.10; IBS was common in women with OSA/H), but was greatly strengthened for bruxism (p value decreased from 0.16 to 0.05). On the whole, the impression from Table 3 is that the prevalence of the indicated symptoms/signs increases as severity of AHI decreases.

Discussion

In this series of patients with sleep-disordered breathing, we have investigated the relationship between the severity of sleep-disordered breathing and the prevalence of a variety of symptoms/signs, many of which are associated with functional somatic syndromes. We have found that the percentage of women and the prevalence of sleep-onset insomnia, headache, IBS, and alpha-delta sleep are high among patients with UARS and decrease progressively with increasing severity of sleep-disordered breathing. These symptoms/signs appear to be widely distributed among patients with sleep-disordered breathing rather than restricted to a particular subgroup. The prevalence differences in the various symptoms/signs remained largely intact when differences between the groups in gender distribution were accounted for. These findings confirm our impression that UARS differs from moderate-to-severe OSA/H in its symptoms/signs, and it shares common symptoms/signs with the functional somatic syndromes.

In our previous study of upper airway collapsibility in patients with UARS and OSA/H, we found that patients with UARS, mild-to-moderate OSA/H, and moderate-to-severe OSA/H represent a continuum of increasing upper airway collapsibility.[2] Our findings in this study suggest that the symptoms/signs of sleep-disordered breathing also constitute a continuum. At the extremes of sleep-disordered breathing severity (UARS vs moderate-to-severe OSA/H), we found clear differences in clinical features. Our UARS patients were 50% female, with a high prevalence of sleep-onset insomnia, headache, IBS, and alpha-delta sleep. In contrast, our patients with moderate-to-severe OSA/H were 8% female, with a lower prevalence of sleep-onset insomnia, headache, IBS, and alpha-delta sleep. Consistent with a continuous progression of symptom/sign prevalence, our patients with mild-to-moderate OSA/H were 20% female, with an intermediate prevalence of sleep-onset insomnia, headache, IBS, and alpha-delta sleep. These findings suggest that the physiologic continuum of upper airway collapsibility during sleep that characterizes sleep-disordered breathing is paralleled by a continuous progression of the prevalence of symptoms/signs. There does not appear to be a discrete UARS.

While it is evident that the prevalence of symptoms/signs among patients with sleep-disordered breathing of varying severity constitutes a continuous progression, the direction of that progression appears counterintuitive. In patients with the least severe sleep-disordered breathing (UARS), the prevalence of sleep-onset insomnia, headaches, IBS, and alpha-delta sleep is highest, while in patients with the most severe sleep-disordered breathing (moderate-to-severe OSA/H), the prevalence of the same symptoms is lowest. Why does the prevalence of sleep-onset insomnia, headache, IBS, and alpha-delta sleep decrease as the severity of sleep-disordered breathing increases? Although our data do not answer this question, they may provide a clue. The increased prevalence of alpha-delta sleep in patients with UARS indicates that the quality of their sleep is different from that of patients with moderate-to-severe OSA/H. In pa-

Table 3—*Relationship Between Gender and the Prevalence of Symptoms/Signs**

Variables	Sleep-Onset Insomnia		Headache		IBS		Alpha-Delta Sleep		Bruxism	
	F	M	F	M	F	M	F	M	F	M
UARS	23	60	53	60	53	30	23	25	38	67
Mild-to-moderate OSA/H		15		30		15		10		35
	28		14		43		14		14	
Moderate-to-severe OSA/H		10		17		17		0		35
	(p = 0.04)		(p = 0.01)		(p = 0.10)		(p = 0.02)		(p = 0.05)	

*Data are presented as %. Because only seven women had OSA/H, we did not subdivide women with OSA/H into AHI groups. p values were obtained using the CMH test of zero correlation controlled for gender. F = female; M = male.

tients with functional somatic syndromes, the marked intrusion of alpha rhythm into slow-wave sleep is known to be associated with alpha intrusion into other NREM sleep stages and a high frequency of subjective sleep complaints.[24] Therefore, alpha-delta sleep may represent a diminution in the quality of sleep of patients with UARS. The adulterated sleep of patients with UARS may explain their complaints of sleep-onset insomnia, and it may contribute to autonomic dysfunction manifested as headache and IBS. The reason for the increasing prevalence of alpha-delta sleep, sleep-onset insomnia, headache, and IBS with decreasing severity of AHI warrants further study.

While our study indicates a difference between the symptoms/signs of UARS and those of moderate-to-severe OSA/H, we have no data comparing the symptoms/signs of UARS with those of gender-matched outpatients without sleep-disordered breathing. Such a comparison is needed to know whether the symptoms/signs more prevalent in patients with UARS result from inspiratory flow limitation during sleep. It is possible that having moderate-to-severe OSA/H protects against having functional somatic syndrome symptoms/signs. The absence of the symptoms/signs in a gender-matched group of outpatients without sleep-disordered breathing would suggest that inspiratory flow limitation during sleep is needed for the development of functional somatic syndrome symptoms/signs. Unfortunately, finding a gender-matched sample of outpatients known to be without sleep-disordered breathing was beyond the scope of our study. Thus, we cannot be certain that the symptoms/signs associated with UARS are unique to patients with inspiratory airflow limitation during sleep.

The presence of alpha-delta sleep in several of our patients with UARS and the apparent comorbidity between UARS and the functional somatic syndromes led to our interest in examining the relationship between the severity of sleep-disordered breathing and the functional somatic syndrome symptoms/signs. Patients with functional somatic syndromes constitute a large group seen by internists specializing in rheumatology, infectious disease, and gastroenterology, and by mental health professionals. In the United Kingdom, it is estimated that functional somatic syndrome symptoms constitute 20 to 25% of the complaints of patients seen in outpatient internal medicine practices.[11] The functional somatic syndromes are a large group of disorders of uncertain etiology. Included among these syndromes are chronic fatigue syndrome, fibromyalgia, IBS, temporomandibular joint syndrome, and migraine/tension headache syndrome. The syndromes affect female patients more commonly than male patients and tend to overlap, sharing many common symptoms/signs. Among these symptoms are fatigue, sleep-onset and maintenance insomnia,[7,13] unrefreshing sleep,[12,13] EEG anomalies during sleep,[5–6,20] body pain and tenderness,[12,13,15,18] heartburn, abdominal pain/urgency and diarrhea,[14,15] headaches,[7,12,16] and depression.[13,16] Treatment of the functional somatic syndromes is largely symptomatic and of limited efficacy, relying heavily on analgesics, psychotropic medication, physical therapy, and psychotherapy.[9,11] Thus, the symptoms/signs of patients with UARS are similar to those of a large group of patients with syndromes of uncertain etiology whose treatments are of limited efficacy.

The functional somatic syndromes are thought to be multiaxial syndromes in which psychological factors (depression), neurologic factors (increased pain sensitivity), hormonal factors (orthostatic hypotension and alterations in the hypothalamic-pituitary-adrenal axis), and sleep-related factors (frequent arousals and alpha frequency intrusion into sleep) interact to produce a complex clinical presentation.[25] By demonstrating that the symptoms/signs of UARS resemble those of the functional somatic syndromes, we have introduced the possibility that unrecognized inspiratory flow limitation during sleep plays a role in the development of functional somatic syndromes. Specifically, the frequent arousals and alpha wave intrusion into the sleep of patients with functional somatic syndromes and the nonrestorative sleep associated with these syndromes may result from inspiratory flow limitation. Determining if inspiratory flow limitation during sleep causes the sleep fragmentation of the functional somatic syndromes will require further study.

While the significance of finding the symptoms of functional somatic syndromes in patients with sleep-disordered breathing is uncertain, several studies have found a high prevalence of sleep-disordered breathing in samples of patients with functional somatic syndromes. Buchwald and associates[26] studied the sleep of patients with chronic fatigue syndrome and found that nearly half of these patients had OSA/H. Kumar and associates[27] studied the sleep of patients with IBS and observed OSA/H in three of six patients with IBS, but in none of six control subjects. In studies of the sleep of patients with fibromyalgia, investigators have demonstrated the presence of recurrent oxyhemoglobin desaturations,[28] periodic breathing,[29] and OSA/H.[21] All of the previous studies screened patients for OSA/H as the only manifestation of sleep-disordered breathing. Had previous investigators screened patients for milder inspiratory airflow limitation, it is possible that they would have observed an even stronger asso-

ciation between sleep-disordered breathing and the functional somatic syndromes.

Although our study provides useful information concerning the clinical presentation of sleep-disordered breathing, our methods have a limitation. Specifically, we did not confirm each patient's medical history by obtaining the patient's medical record. We do not believe, however, that our study is greatly limited by this factor. Nearly all the patients utilizing our suburban, sleep-disorders center are sophisticated individuals with health insurance and primary care providers. Thus, our patients had ready access to evaluation of their health-related complaints and knowledge of their medical histories. Moreover, for subjective symptoms like sleep-onset insomnia, headache, and IBS, obtaining the medical record would provide little support for the patients' histories. Thus, we do not believe that our not obtaining the patients' medical records limits the conclusions that we can drew from this study.

The sample size of our study (75 patients) limited our capacity to control for covariance and limited the conclusions we can draw from our data. Although we were able to control for gender, we were not able to concomitantly control for BMI, which increased with increasing AHI group. It can be argued, however, that while it is necessary to control for gender differences (because gender is known to be correlated with the symptoms/signs of the functional somatic syndromes), it is not necessary to control for BMI. Differences in BMI have not been associated with the prevalence of functional somatic syndrome symptoms/signs. Nevertheless, our sample size does limit our capacity to be certain that the AHI (and not other factors) is responsible for the prevalence of the symptoms/signs of the functional somatic syndromes in patients with sleep-disordered breathing.

In conclusion, our findings suggest that the clinical presentation of UARS differs from that of moderate-to-severe OSA/H, while it resembles the clinical presentation of the functional somatic syndromes. Our findings, however, do not prove that the functional somatic syndromes are caused by inspiratory flow limitation during sleep. Rather, they raise many questions. How are upper airway collapse during sleep and symptoms/signs such as sleep-onset insomnia, headaches, IBS, and alpha-delta sleep related? How would treatment of sleep-disordered breathing affect concomitant symptoms/signs other than sleepiness/fatigue? Does unrecognized inspiratory airflow limitation play a role in the functional somatic syndromes? The answers to these questions may lead to improvements in the diagnosis and management of sleep-disordered breathing and the functional somatic syndromes.

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APPENDIX B

Upper Airway Collapsibility During Sleep in Upper Airway Resistance Syndrome*

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Study objectives: To compare upper airway collapsibility during sleep between patients with upper airway resistance syndrome (UARS), normal subjects, and patients with obstructive sleep apnea/hypopnea syndrome (OSA/H).
Design: A descriptive study of a series of clinical patients and a cohort of normal control subjects.
Setting: Two academic sleep-disorders centers.
Patients or participants: One hundred six adult patients with sleep-disordered breathing evaluated at the SUNY Sleep Disorders Center–Medicine and 12 adult subjects without habitual snoring or daytime sleepiness and with an apnea/hypopnea index (AHI) < 5/h evaluated at the Johns Hopkins Pediatric Sleep Disorders Center.
Interventions: All subjects underwent full-night polysomnography and a determination of pharyngeal critical pressure (Pcrit). All patients had a determination of therapeutic level of nasal continuous positive airway pressure (Ptherapeutic).
Measurements and results: The mean ± SD Pcrit of the 12 normal subjects was − 15.4 ± 6.1 cm H_2O; the mean Pcrit of the 22 UARS patients was − 4.0 ± 2.1 cm H_2O; the mean Pcrit of the 37 patients with mild-to-moderate OSA/H (AHI ≥ 10/h and < 40/h) was − 1.6 ± 2.6 cm H_2O; and the mean Pcrit of the 47 patients with moderate-to-severe OSA/H (AHI ≥ 40/h) was 2.4 ± 2.8 cm H_2O. The Pcrit of each group differed from that of all other groups ($p < 0.01$). The mean Ptherapeutic of patients with UARS was 6.9 ± 1.7 cm H_2O; the mean Ptherapeutic of patients with mild-to moderate OSA/H was 7.9 ± 1.9 cm H_2O ($p = 0.08$ compared with the Ptherapeutic of UARS patients); and the mean Ptherapeutic of patients with moderate-to severe OSA/H was 10.5 ± 2.4 cm H_2O ($p < 0.0001$ compared to each of the other patient groups).
Conclusion: UARS is a syndrome of increased upper airway collapsibility during sleep. The upper airway collapsibility during sleep of patients with UARS is intermediate between that of normal subjects and that of patients with mild-to moderate OSA/H.

(CHEST 2002; 121:1531–1540)

Key words: inspiratory flow limitation; nasal continuous positive airway pressure; obstructive sleep apnea; pharyngeal critical pressure; upper airway resistance syndrome

Abbreviations: AT/ET = mean apnea time/event time; BMI = body mass index; CPAP = continuous positive airway pressure; MSLT = multiple sleep latency test; NREM = nonrapid eye movement; OSA/H = obstructive sleep apnea/hypopnea syndrome; Pcrit = pharyngeal critical pressure; ΔPesoph = change in esophageal pressure; Pmask = nasal mask pressure; Ptherapeutic = therapeutic level of nasal continuous positive airway pressure; Rus = airway resistance between the nares and the point of collapse under conditions of inspiratory flow limitation; SWS = slow-wave sleep; UARS = upper airway resistance syndrome; UPPP = uvulopalatopharyngoplasty; Vimax = maximal inspiratory airflow

Clinical investigators have recognized that inspiratory flow limitation with arousal from sleep may be a cause of daytime fatigue and sleepiness even in the absence of obstructive sleep apnea/hypopnea syndrome (OSA/H). Patients with upper airway resistance syndrome (UARS) have periods of sleep associated with inspiratory flow limitation, increased inspiratory effort, and arousal.[1] Preventing inspiratory flow limitation in patients with UARS with nasal continuous positive airway pressure (CPAP) results in a decrease in their frequency of arousals and an improvement in their daytime fatigue and sleepiness.[1] Therefore, understanding the pathophysiology

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of UARS is important to the management of patients with sleep-disordered breathing.

Although UARS has become widely recognized, its relationship to normal respiration during sleep and to OSA/H remains uncertain. Some investigators[2] maintain that UARS is a condition of the upper airway that is distinct from the upper airway of OSA/H patients. Their position is based on differences in the demographics and clinical presentations they have observed between patients with UARS and patients with OSA/H. Others[3] maintain that UARS is an artifact resulting from the imprecise measurement of airflow with thermal sensors during clinical sleep studies. They suggest that if airflow were more precisely quantified with pressure transducers and pneumotachographs, the diagnosis of UARS would become obstructive sleep hypopnea. Thus, the issue of whether UARS is a distinct physiologic entity or an artifact of polysomnographic technology is unresolved.

Modeling upper airway function during sleep may allow the comparison of upper airway function between individuals with normal breathing, patients with UARS, and patients with OSA/H. Physiologic study of the upper airway during sleep in normal subjects[4] and in patients with OSA/H[5] has shown that in both conditions, the upper airway behaves like a Starling resistor.[6] Accordingly, inspiratory airflow through the upper airway during sleep is determined by the pressure at which a flow-limiting site within the upper airway collapses. The airway pressure at the flow-limiting site below which the flow-limiting site collapses, the pharyngeal critical pressure (Pcrit), has been used as an index of upper airway collapsibility.[7] Previous studies[4,8] have demonstrated that normal subjects, primary snorers, patients with obstructive sleep hypopnea, and patients with obstructive sleep apnea are distinguished by progressively higher values of Pcrit, signifying progressively more collapsible upper airways. Patients with UARS resemble normal subjects in having little apnea and hypopnea during sleep, but also resemble OSA/H patients in having sleep fragmentation and fatigue or sleepiness. Because patients with UARS have a clinical presentation that is intermediate between normal subjects and patients with OSA/H, we hypothesize that their upper airway collapsibility and Pcrit values are intermediate between those of the two groups. Applying the Starling resistor model to upper airway function in UARS, therefore, may enable us to determine whether UARS is a state of upper airway collapsibility intermediate between that of normal subjects and patients with OSA/H. To compare upper airway collapsibility during sleep between normal subjects, patients with UARS, and patients with OSA/H, we compared the upper airway pressure-flow relationships during sleep of the three groups using the Starling resistor model of upper airway function.

Materials and Methods

Study Population

One hundred six adult patients with sleep-disordered breathing who completed sleep evaluations at the SUNY Sleep Disorders Center–Medicine constitute the patient sample (UARS and OSA/H patients). The patients all had initial consultations and were selected only for having completed standard evaluations as detailed below. We obtained a cohort of 12 adult normal subjects from participants in a study of developmental changes in upper airway pressure and airflow dynamics during sleep. The normal subjects were studied at the Johns Hopkins University Pediatric Sleep Disorders Center. Publication of the patient data was approved by the Institutional Review Board of the State University of New York–Stony Brook. The study of developmental changes in upper airway pressure and airflow dynamics was approved by the Institutional Review Board of Johns Hopkins University.

UARS

We used a diagnostic standard comparable to that of Guilleminault and associates:[1] All of our UARS patients met the following criteria: (1) they requested a sleep consultation for daytime fatigue and sleepiness; (2) their fatigue or sleepiness did not result from diagnoses of OSA/H (apnea hypopnea index [AHI] < 10/h), narcolepsy, or periodic leg movements syndrome; and (3) their fatigue or sleepiness was associated with inspiratory flow limitation with arousals from sleep, while breathing at atmospheric pressure during a nasal CPAP titration study. The level of sleepiness as assessed by the multiple sleep latency test (MSLT) or the Epworth Sleepiness Scale, the frequency of arousals not associated with apnea and hypopnea during polysomnography, and the presence or absence of habitual snoring were not used as diagnostic criteria.

Normal Subjects

Healthy adult subjects without habitual snoring and without sleepiness were recruited from the general community. Subjects underwent full-night polysomnography, and only subjects with an AHI ≤ 5/h were included.

Evaluation of Sleep-Disordered Breathing

The patients with sleep-disordered breathing were each evaluated with the routine clinical sleep evaluation performed at the SUNY Sleep Disorders Center–Medicine. The evaluation began with a general medical and sleep-related history and physical examination. Patients were questioned regarding symptoms of narcolepsy and restless legs syndrome. Patients with a diagnosis of narcolepsy as determined by a history of cataplexy or by a sleep latency of < 5 min with two rapid eye movement onset naps during the MSLT[9] were excluded from the diagnosis of UARS.

Distinguishing patients with UARS from patients with periodic leg movements syndrome can be difficult because both can have leg movements and arousals associated with minimal changes in airflow as determined by a thermocouple. Therefore, after the exclusion of narcoleptics, all patients complaining of fatigue or

sleepiness who did not meet our criteria for OSA/H remained candidates for the diagnosis of UARS. A nasal CPAP titration study was performed to identify the patients with inspiratory flow limitation at atmospheric pressure (UARS patients) and to determine their therapeutic CPAP. Patients with leg movements but without inspiratory flow limitation or patients who continued to have leg movements at the therapeutic level of nasal CPAP (Ptherapeutic) received a diagnosis of periodic leg movement syndrome.

Normal subjects were evaluated by polysomnography at the Johns Hopkins Pediatric Sleep Disorders Center. Polysomnography that was performed at the Johns Hopkins Pediatric Sleep Disorders Center did not differ significantly in its performance or its analysis from that performed at the SUNY Sleep Disorders Center–Medicine.

Full-Night Polysomnography

At the SUNY Sleep Disorders Center–Medicine, standard full-night polysomnography was performed. Sleep stages were monitored using surface EEG activity of the central and occipital regions, submental surface electromyographic activity, and left and right electro-oculographic activity. Leg movement was detected using surface electromyographic activity of the right and left tibialis anterior muscle. Airflow at the nose and mouth was monitored with a thermocouple. Thoracoabdominal movement was monitored with piezoelectric belts. Oxyhemoglobin saturation was monitored at the finger using a pulse oximeter. A continuous ECG monitored heart rate and rhythm. All of the data were converted from analog to digital and stored on a computer for analysis by an American Board of Sleep Medicine-certified sleep physician.

Sleep was staged using the scoring system of Rechtschaffen and Kales[10] with the modifications of Flagg and Coburn[11] for sleep-disordered breathing. EEG arousals not associated with hypopnea or apnea were identified using the American Academy of Sleep Medicine Task Force criteria.[12] For each patient, the total of arousals not associated with hypopnea or apnea was divided by the total sleep time to derive an arousal index (arousals per hour).

We quantified an AHI for each patient. Apnea was defined as a decrease of inspiratory airflow to $< 20\%$ of waking levels. Hypopnea was defined as a decrease in inspiratory airflow to $< 50\%$ of waking levels. An apnea/hypopnea event was defined as apnea lasting 10 s or any combination of apnea and hypopnea lasting 10 s and ending with an arousal. In addition to determining an AHI, we characterized each patient's tendency to apnea within his disordered breathing events. To accomplish this, we measured the apnea time of each event and determined a ratio of apnea time to event time. We expressed each patient's tendency to apnea within disordered breathing events as his mean apnea time/event time (AT/ET).

The diagnosis of OSA/H was established by an AHI of at least 10 events per hour of sleep. For purposes of data analysis, the OSA/H patients were classified into groups of mild-to-moderate OSA/H (AHI $\geq$ 10/h and $<$ 40/h) and moderate-to-severe OSA/H (AHI $\geq$ 40/h).

Nasal CPAP Study

Every patient with OSA/H and possible UARS underwent a nasal CPAP study. During the nasal CPAP study, each patient slept wearing a nasal CPAP mask (Respironics; Murrysville, PA). The mask was attached via a breathing circuit and a bi-directional valve to a source of CPAP and to a source of negative pressure (a modified Rem-Star unit; Respironics). Using the dual-pressure sources, we were able to vary the nasal mask pressure (Pmask) between + 20 cm H_2O and − 20 cm H_2O. The monitoring of sleep stages, leg movements, heart rhythm, and oxyhemoglobin saturation during the nasal CPAP study was the same as for full-night polysomnography. Nasal airflow was measured with a heated pneumotachograph (model 3813; Hans Rudolph; Kansas City, MO) and transducer (model MP45-14-871; Validyne Engineering; Northridge, CA) interposed between the bi-directional valve and the nasal mask. Inspiratory effort was measured as a change in esophageal pressure (ΔPesoph) using a balloon-tipped catheter with side ports in its distal 5 cm. The distal 5 cm was positioned in the middle third of the esophagus. Pmask was monitored directly from a port in the mask. Both ΔPesoph and Pmask were measured by a differential pressure transducer (model 23ID; Spectramed; Oxnard, CA) referenced to atmosphere.

In the SUNY Sleep Disorders Center–Medicine sleep laboratory, the purpose of the nasal CPAP study varies with the underlying diagnosis. For patients with OSA/H, the study determines the Ptherapeutic. We define the Ptherapeutic as the Pmask at which inspiratory flow limitation resolves or ΔPesoph is minimized.

For patients with a complaint of daytime fatigue sleepiness but without a diagnosis of OSA/H or narcolepsy, the CPAP study establishes a diagnosis of UARS. A diagnosis of UARS requires that a patient demonstrate inspiratory flow limitation at a Pmask of atmospheric pressure (between + 1 cm H_2O and − 1 cm H_2O). Inspiratory flow limitation is considered to occur when inspiratory flow plateaus despite an esophageal pressure that continues to decrease (Fig 1). When inspiratory flow limitation is demonstrated at atmospheric Pmask, we characterize the airflow dynamics by measuring both the maximal inspiratory flow ($\dot{V}$Imax) and the inspiratory ΔPesoph for five to eight consecutive breaths during continuous nonrapid eye movement (NREM) sleep. Pmask is then progressively increased in 1-cm H_2O increments while inspiratory flow and effort are monitored until Ptherapeutic is reached (Fig 2).

Pcrit Determination

Pcrit was determined during the nasal CPAP study using a steady-state method[7] (Fig 3, 4). For patients with Pcrit greater than atmospheric pressure, we determined the Pcrit by gradually increasing the Pmask to the lowest pressure at which each inspiratory effort was associated with inspiratory flow limitation during stage 2 sleep (between a sleep spindle or K complex and the next arousal). After 30 s at that pressure, we recorded $\dot{V}$Imax for several breaths with the patient's mouth closed. We continued to raise the Pmask in 1-cm H_2O increments and repeated the $\dot{V}$Imax measurements at two more levels of Pmask associated with inspiratory flow limitation. Pcrit was determined by regressing $\dot{V}$Imax on Pmask and solving for Pmask at $\dot{V}$Imax of 0 mL/s. The airway resistance upstream to the flow-limiting site (the airway resistance between the nares and the point of collapse under conditions of inspiratory flow limitation [Rus]) was determined as the reciprocal of the slope of the regression.[7] For patients with Pcrit less than atmospheric pressure, we determined the Pcrit by gradually decreasing the Pmask and measuring $\dot{V}$Imax as described above. We continued to decrease Pmask until $\dot{V}$Imax was sampled at three levels of Pmask.

To increase the accuracy of our Pcrit determinations, we accepted a Pcrit determination only if we were able to achieve values of $\dot{V}$Imax $<$ 100 mL/s. In addition, we used $\dot{V}$Imax data from the three lowest levels of Pmask for the Pcrit regression. These criteria improved the accuracy of our measurements in two ways. First, by using values of Pmask close to Pcrit, we minimized the loss of upper airway muscle activity that accompanies higher

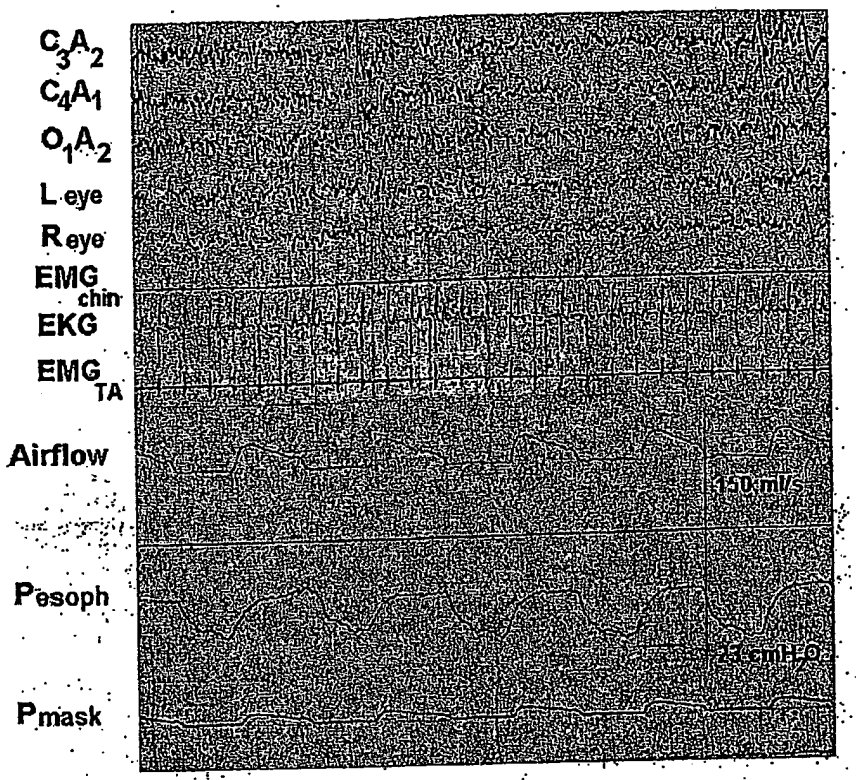

FIGURE 1. A 30-s epoch of a nasal CPAP study in a patient with UARS (patient EX) with Pmask at 1 cm H_2O (atmospheric pressure). The airflow channel illustrates a plateau of inspiratory flow (down) at 150 mL/s. Pesoph (representing the driving pressure for inspiration) continues to decrease beyond the plateau in inspiratory airflow indicating inspiratory flow limitation (vertical line). The total esophageal pressure excursion (inspiratory effort) is 23 cm H_2O. L = left; R = right; EMG = electromyogram; EKG = electrocardiogram; TA = tibialis anterior.

levels of CPAP.[13] Decreasing upper airway muscle activity could increase the collapsibility and Pcrit being measured. Second, by keeping our lowest values of $\dot{V}$max < 100 mL/s, we narrowed the 95% confidence interval for the value of Pmask at $\dot{V}$max = 0 (the Pcrit; Fig 4).[14]

The Pcrit determinations done at the Johns Hopkins Pediatric Sleep Disorders Center differed slightly from the determinations done at the SUNY Sleep Disorders Center–Medicine. Although the same dual pressure source/pneumotachograph system was used, esophageal pressure was not used as an indicator of inspiratory effort. The subject was allowed to fall asleep receiving a low level of positive pressure (2 to 4 cm H_2O). Pmask was then lowered in 2-cm H_2O decrements until either upper airway occlusion occurred, the patient aroused from sleep, or a minimum pressure of − 20 cm H_2O had been applied. Under conditions of inspiratory flow limitation, multiple measurements of $\dot{V}$max were made as a function of Pmask. Pcrit and Rus were determined using the same regression used for the sleep-disordered breathing patients. Inspiratory flow limitation was considered to occur when a characteristic inspiratory flow waveform occurred (increasing inspiratory flow followed by a mid-inspiratory plateau).[15,16] Measurements were performed during slow-wave sleep (SWS). When measurements during SWS were not possible (due to sleep stage transitions or lack of SWS in the laboratory situation), measurements were performed during stage 2 sleep.

Statistical Analysis

Differences in gender distribution between the four groups (normal subjects, UARS, mild-to-moderate OSA/H, moderate-to-severe OSA/H) were tested overall and in pairwise fashion by Fisher Exact Test. Differences among the groups in mean age, body mass index (BMI), Pcrit, Ptherapeutic (in the three patient groups), and Rus were tested overall with a one-way analysis of variance F test followed by pairwise *t* tests within the analysis of variance. All other statistical tests compared patients with UARS to only one other group or compared UARS patient data before and after intervention. These comparisons were all done as *t* tests (paired and unpaired as appropriate).

RESULTS

The anthropometric data for normal subjects and sleep-disordered breathing patients are given in Table 1. The normal subjects were younger than each of the sleep-disordered breathing groups ($p < 0.01$). They were not obese, with a BMI significantly lower than each of the sleep-disordered breathing groups ($p < 0.01$). They were predominantly female, with a

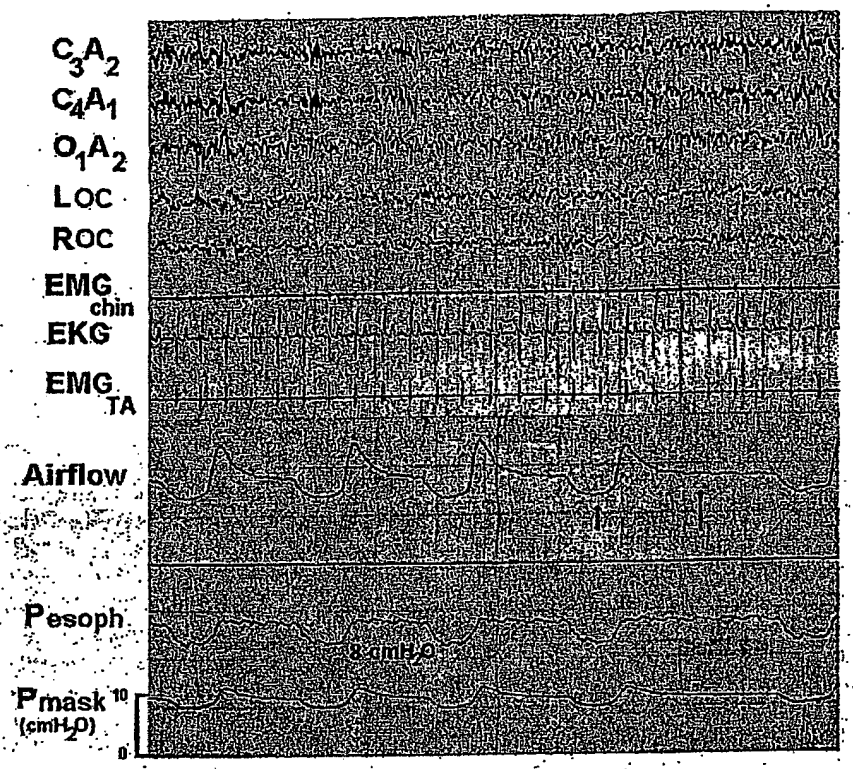

FIGURE 2. A 30-s epoch of a nasal CPAP study in a patient with UARS (patient EX) with Pmask at 10 cm H_2O (Ptherapeutic). The respiratory pattern is no longer that of inspiratory flow limitation. The cardiac artifact in the airflow signal during both expiration (long arrow) and inspiration (short arrow) proves that airflow varies with changes in driving pressure throughout the respiratory cycle. Inspiratory effort (8 cm H_2O) is greatly reduced from the levels observed at atmospheric pressure (Fig 1). LOC = left outer canthus; ROC = right outer canthus; see Figure 1 legend for expansion of abbreviations.

gender distribution that was significantly different from each of the predominantly male sleep-disordered breathing groups ($p < 0.05$).

The three groups of sleep-disordered breathing patients differed in two aspects (Table 1). First, the group with moderate-to severe OSA/H was more obese than either of the other two groups ($p < 0.001$). Second, the percentage of women in the groups decreased with increasing AHI, although only the difference between patients with UARS and patients with moderate-to severe was statistically significant ($p = 0.03$).

Our 12 normal subjects had a mean ± SD AHI of 0.1 ± 0.1/h and an arousal index (arousals unrelated to apneas and hypopneas) of 12.3 ± 7.9/h. The 22 patients with UARS had an mean AHI of 3.8 ± 3.1/h, which was significantly greater than that of the normal subjects ($p = 0.0003$). Their mean arousal index was 23.2 ± 12.5/h, which was significantly greater than that of the normal subjects ($p = 0.01$). The 37 patients with mild-to-moderate OSA/H had a mean AHI of 23.9 ± 7.8/h and a mean arousal index of 15.3 ± 10.3/h. The 47 patients with moderate-to severe OSA/H had an AHI of 71.6 ± 20.5/h and an arousal index of 5.0 ± 8.4/h.

While breathing at Pmasks approximating atmospheric pressure during the nasal CPAP study, all of the patients with UARS consistently experienced inspiratory flow limitation during NREM sleep (Fig 1). The mean $\dot{V}$Imax for the patients with UARS was 191 ± 83 mL/s, and the mean inspiratory ΔPesoph was 16 ± 8 cm H_2O. At Ptherapeutic (Fig 2), the mean inspiratory ΔPesoph for the group was 5 ± 4 cm H_2O, representing an 11-cm H_2O decrease in inspiratory effort at Ptherapeutic ($p < 0.0001$).

The Pcrit values for the normal subjects and the three groups of patients with sleep-disordered breathing are shown in Figure 5. The mean Pcrit of normal subjects was − 15.4 ± 6.1 cm H_2O; mean Pcrit of UARS patients was − 4.0 ± 2.1 cm H_2O;

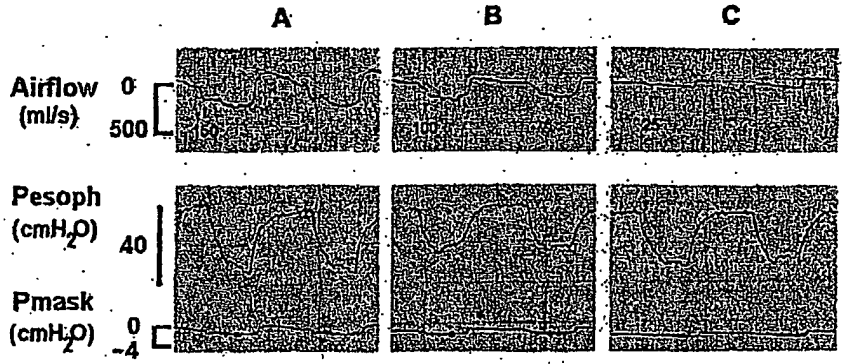

FIGURE 3. Relationship between airflow (inspiration is down), esophageal pressure (Pesoph), and Pmask during NREM for Pcrit determination in patient EX. As Pmask is decreased from − 0.8 cm H_2O (*left, A*) to − 1.6 cm H_2O (*center, B*) and − 2.6 cm H_2O (*right, C*), $\dot{V}$max progressively decreases as shown (labeled arrows).

mean Pcrit of patients with mild-to-moderate OSA/H was − 1.6 ± 2.6 cm H_2O; and mean Pcrit of patients with moderate-to-severe OSA/H was 2.4 ± 2.8 cm H_2O. The difference in Pcrit between any two of the groups was statistically significant ($p < 0.01$). The mean Rus of normal subjects was 21.5 ± 9.5 cm H_2O/L/s; the mean Rus of the UARS patients was 21.4 ± 6.5 cm H_2O/L/s (not significant compared to normal subjects); the mean Rus of patients with mild-to-moderate OSA/H was 19.2 ± 7.9 cm H_2O/L/s (not significant compared with the normal subjects and UARS patients); and the mean Rus of patients with moderate-to-severe OSA/H patients was 15.6 ± 8.4 cm H_2O/L/s (significantly lower than the normal subjects and patients with UARS; $p < 0.03$). Thus, patients with UARS demonstrated upper airway collapsibility that was intermediate between that of normal subjects and of patients with mild-to-moderate OSA/H. In addition, as AHI increased in patients with sleep-disordered breathing, upper airway collapsibility also increased. Finally, the Rus of normal subjects and patients with UARS were similar, but Rus tended to decrease with increasing AHI in patients with sleep-disordered breathing.

The three groups of patients with sleep-disordered breathing were characterized by progressively increasing Ptherapeutic values. The mean Ptherapeutic of patients with UARS was 6.9 ± 1.7 cm H_2O; the mean Ptherapeutic of patients with mild-to-moderate OSA/H was 7.9 ± 1.9 cm H_2O; and the mean Ptherapeutic of patients with moderate-to-severe OSA/H was 10.5 ± 2.4 cm H_2O. While the difference in Ptherapeutic values between the patients with UARS and patients with mild-to-moderate OSA/H did not reach statistical significance ($p = 0.08$), both differed significantly from the group with moderate-to-severe OSA/H ($p < 0.0001$).

Because the normal subjects were significantly younger, leaner, and more often female than patients with sleep-disordered breathing, we further examined the relationship between Pcrit and subject group in subgroups of patients based on gender, age (< 40 years vs ≥ 40 years), and BMI (< 30 vs ≥ 30). Table 2 demonstrates that in every instance but one (female patients with moderate-to-severe OSA/H; n = 2), the Pcrit increased as the severity of sleep-disordered breathing increased. These findings suggest that the severity of sleep-disordered breathing,

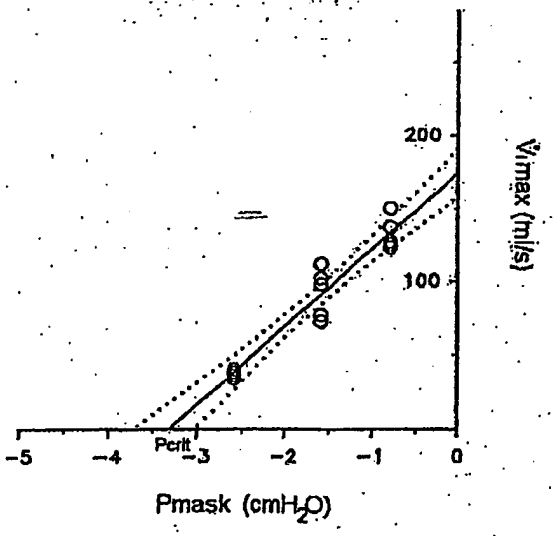

FIGURE 4. Regression of $\dot{V}$max on Pmask to derive Pcrit (the X intercept) of patient EX. The dotted lines are the 95% confidence interval for the slope of the regression. By regressing values of $\dot{V}$max that are close to 0 mL/s, we decrease the 95% confidence interval for the x intercept (the Pcrit). Thus, the Pcrit is − 3.3 cm H_2O (95% confidence interval, − 3.0 to − 3.7 cm H_2O).

Table 1—*Anthropometric Data**

Variables	Normal Subjects	UARS	Mild-to-Moderate OSA/H	Moderate-to-Severe OSA/H
Patients, No.	12	22	37	47
Age, yr	34 (8)†	47.5 (14.5)	53 (12)	51 (12)
BMI, kg/m^2	24 (3)†	31 (8)	33 (6)	38 (8)§
Male/female gender, No.	4/8†	17/5	31/6	45/2‖

*Data are presented as mean (SD) unless otherwise indicated.
†$p < 0.01$ compared with each of the sleep-disordered breathing groups.
‡$p < 0.05$ compared with each of the sleep-disordered breathing groups.
§$p < 0.0001$ compared with both UARS and mild to moderate OSA/H groups.
‖$p = 0.03$ compared with UARS patients.

and not gender, age, or obesity, was the primary correlate of Pcrit in our subjects.

To compare airway collapsibility between our patients with UARS and those patients with OSA/H with the least collapsible upper airways during sleep (patients with hypopnea predominant), we selected all the patients with OSA/H whose AT/ET was < 0.2. The 13 patients meeting this criteria had an AHI of 32 ± 17/h and an AT/ET of 0.11 ± 0.05 (hypopnea was 89% of the time spent in sleep-disordered breathing). The mean Pcrit value of this group was − 2.1 ± 2.0 cm H_2O, which was significantly higher than the value for UARS patients (− 4.0 ± 2.1; $p = 0.01$). Thus, in our patients, the diagnosis of UARS identified a group with upper airway collapsibility that was lower than that of patients with OSA/H with the least collapsible upper airways during sleep.

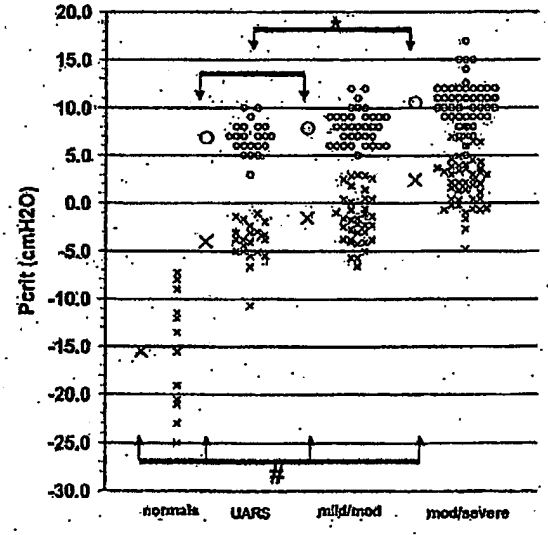

FIGURE 5. Pcrit and Ptherapeutic values for our patients with sleep-disordered breathing and the Pcrit values for our normal subjects (normals). Pcrit values are designated by ×, and Ptherapeutic values are designated by circles. Large markers represent mean values. The mean Pcrit value for each group is significantly different from the mean Pcrit value for all other groups (#$p < 0.01$). The mean Ptherapeutic value for patients with UARS and patients with mild-to-moderate OSA/H did not differ significantly ($p = 0.08$), but both differed significantly from the Ptherapeutic of patients with moderate-to-severe OSA/H. *$p < 0.0001$; mod = moderate.

Discussion

In this study, we have confirmed previous observations[1] that patients with UARS experience inspiratory flow limitation throughout NREM sleep. Further, we have quantified maximal inspiratory airflow and inspiratory effort during NREM sleep in UARS patients and demonstrated that therapeutic nasal CPAP significantly lowers their inspiratory effort. We have used the Starling resistor model of the upper airway during sleep to compare airway collapsibility between normal subjects, patients with UARS, and patients with OSA/H. Comparisons of both Pcrit values and Ptherapeutic values demonstrate that the inspiratory flow limitation of patients with UARS is associated with upper airway collapsibility that is intermediate between that of normal subjects and patients with mild-to-moderate OSA/H.

In choosing to compare collapsibility between groups by comparing their Pcrit values, we have chosen a parameter that is determined once in each subject during a single night's sleep. What is the evidence that Pcrit is a reproducible parameter that reflects upper airway collapsibility over time? The reproducibility of single Pcrit measurements within subjects has been demonstrated, by Schwartz and associates[17,18] in studies of the effects of weight loss and uvulopalatopharyngoplasty (UPPP) on airway collapsibility. In their studies, patients who responded to weight loss or UPPP with a decrease in AHI also had a decrease in Pcrit. Patients who did not lose weight or who did not respond to UPPP with a decrease in AHI had little change in Pcrit values over several months. Therefore, in choosing a single

Table 2—*Relationship of Pcrit to Subject Group in Subgroups of Gender, Age, and BMI*

Variables	Gender				Age				BMI			
	Male, No.	Pcrit (SD), cm H_2O	Female, No.	Pcrit (SD), cm H_2O	< 40 yr, No.	Pcrit (SD), cm H_2O	≥ 40 yr, No.	Pcrit (SD), cm H_2O	< 30, No.	Pcrit (SD) cm H_2O	≥ 30, No.	Pcrit (SD) cm H_2O
Normal subjects	4	− 17.3 (4.9)	8	− 14.5 (6.8)	8	− 14.3 (6.8)	4	− 17.5 (4.2)	11	− 16.1 (5.9)	1	− 8.0
UARS	17	− 3.5 (1.4)	5	− 5.8 (3.0)	6	− 4.5 (3.3)	16	− 3.8 (1.6)	11	− 4.1 (2.7)	11	− 3.9 (1.3)
Mild-to-moderate OSA/H	31	− 1.7 (2.8)	6	− 0.7 (1.6)	5	− 3.0 (2.0)	32	− 1.3 (2.7)	10	− 2.2 (1.9)	27	− 1.3 (2.8)
Moderate-to-severe OSA/H	45	2.6 (2.6)	2	− 1.6 (4.5)	9	2.2 (3.5)	38	2.6 (2.6)	4	0.2 (3.6)	43	2.5 (2.6)

Pcrit measurement as an index of upper airway collapsibility in this study, we have chosen a parameter that is reproducible within subjects over time.

Although the observed difference in Pcrit values between normal subjects and patients with sleep-disordered breathing suggests a difference in upper airway collapsibility, the finding could have resulted from the collection of Pcrit data in two laboratories with slightly differing methods. The two differences in methods between laboratories were the absence of a Pesoph measurement and the preference for collecting Pcrit data during SWS (rather than stage 2 sleep) at the Johns Hopkins Pediatric Sleep Disorders Center. To assess the comparability of methods between the SUNY and Johns Hopkins Pediatric Sleep Disorders Center, we compared the values obtained in both laboratories with published values of Pcrit obtained in comparable groups at the Johns Hopkins Adult Sleep Disorders Center.[4,5,8] Our normal subjects (studied at the Johns Hopkins Pediatric Laboratory) and our hypopnea predominant patients with moderate-to-severe OSA (studied at SUNY) had Pcrit values that were nearly identical with the published values of comparable groups at the Johns Hopkins Adult Sleep Disorders Center. Thus, we believe that the observed differences in Pcrit values between our normal subjects and our patients with sleep-disordered breathing represent differences in upper airway collapsibility between groups and not methodologic differences between centers.

A strength of this study is our choice of normal subjects from the general population and not from patients presenting with sleep-related complaints. Studies that include individuals from the latter group based on normal values for the MSLT or for sleepiness scales make their determination using tests whose sensitivity for quantifying sleepiness is uncertain. While obtaining normal subjects from the general population requires the screening of large numbers of subjects, the resulting group is more likely to be truly normal regarding symptoms of sleep-disordered breathing. Therefore, our choice of normal subjects from the general population may have enhanced our ability to demonstrate a difference in upper airway collapsibility between normal subjects and patients with sleep-disordered breathing.

In choosing our normal subjects, however, we were unable to match for gender distribution, age, and obesity between normal subjects and our patients with sleep-disordered breathing. To some extent, this limits the conclusions we can draw from our study. Matching for every parameter but the tendency to sleep-disordered breathing would have enabled us to conclude that patients with UARS patients differ from normal subjects only in the level of their upper airway collapsibility during sleep. We

believe that our normal subjects do not greatly limit our study. Our comparison of subgroups based on gender, age, and obesity (Table 2) suggests that the tendency to sleep-disordered breathing (and not the demographic factors) is still the principle determinant of Pcrit in our subjects.

Our finding a difference in upper airway collapsibility between patients with UARS and hypopnea-predominant patients with OSA/H with is novel. The distinction between the two diagnoses was made using a thermocouple to measure airflow. Recent trends have been toward monitoring inspiratory airflow more precisely using inspiratory pressure as a surrogate for airflow. This methodology more accurately demonstrates the plateau of the inspiratory signal characteristic of inspiratory flow limitation.[14] It has been suggested[3] that this methodology is also better at distinguishing between varying levels of airflow in patients with inspiratory flow limitation. Our findings do not support this opinion. Rather, our findings suggest that within a single laboratory, airflow estimated by a thermocouple can distinguish varying levels of inspiratory airflow and distinguish a group of patients with UARS from one with hypopnea-predominant OSA/H.

Although most of our patients with UARS had Pcrit values that were intermediate between normal subjects and patients with mild-to-moderate OSA/H, one of our UARS patients had a Pcrit value in the normal range (−10.7 cm H_2O; Fig 5). This particular patient appears to have had normal upper airway collapsibility, but a high upstream resistance (Rus, 32 cm H_2O/L/s) that increased her inspiratory effort and resulted in inspiratory flow limitation during sleep. Thus, while most patients with UARS have increased upper airway collapsibility relative to normal subjects, occasional patients with UARS truly have increased upper airway resistance.

Whether upper airway collapsibility is measured using Pcrit or Ptherapeutic, our data suggest that in patients with sleep-disordered breathing, upper airway collapsibility progressively increases with increasing AHI. Figure 5 demonstrates, however, that the range of airway collapsibility between patients with UARS and patients with moderate-to-severe OSA/H is greater when measured by Pcrit (6.4 cm H_2O) than when measured by Ptherapeutic (a range of 3.6 cm H_2O). We believe that the difference between the two measurements is caused by a difference in their determinants. Pcrit is affected chiefly by upper airway collapsibility. Ptherapeutic is affected by both the upper airway collapsibility and the upper airway resistance (Rus) between the nares and the flow-limiting site. (Although Ptherapeutic is applied at the nares, it must act at the flow-limiting site.) The greater the Rus, the greater the difference between Ptherapeutic and Pcrit. Therefore, by comparing mean values of Pcrit and Ptherapeutic in our three patient groups (Fig 5), it becomes evident that as Pcrit increases, Rus decreases. This conclusion is supported by the values of Rus that we obtained in our patients with sleep-disordered breathing. The decrease in Rus may be caused by a dilatory effect of higher nasal CPAP pressures (in patients with higher values of Pcrit) on the caliber of the upper airway. Dilation of the upper airway by nasal CPAP should decrease Rus. Thus, while both Pcrit and Ptherapeutic progressively increase with increasing upper airway collapsibility, changes in Pcrit more accurately reflect changes in upper airway collapsibility.

From the perspective of upper airway physiology, our data suggest that UARS patients differ from OSA/H patients only in the degree of their upper airway collapsibility. Our findings, however, do not preclude the possibility that UARS patients differ from OSA/H patients in other important ways. Guilleminault and associates[2] have observed that UARS patients frequently complain of insomnia and fatigue, complaints that are less frequent among patients with OSA/H. In addition, among UARS patients studied by Guilleminault and associates, women comprise 56%. This prevalence of women is much higher than the 10% commonly observed among OSA/H patients.[19,20] Our data support the existence of gender differences between UARS patients and OSA/H patients and they do not preclude the existence of symptom differences between the groups. Our study does not address the question of whether UARS is a unique clinical syndrome associated with modest increases in upper airway collapsibility.

In summary, modeling of the upper airway as a Starling resistor leads to the conclusion that, in most patients, UARS is a condition of mildly increased upper airway collapsibility. Whether the syndrome deserves to be distinguished from OSA/H depends on whether it is associated with discrete symptoms or with a differing prognosis. Further investigation of these possibilities will determine whether there should be a distinct UARS.

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